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EAU Guidelines on

Renal Cell Carcinoma

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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 references/individual circumstances of patients into account. Guidelines are not mandates and do not purport to be a legal standard of care.

1.2 Panel composition

The EAU Guidelines Panel on RCC consists of an international multidisciplinary group of clinicians, including urological surgeons, oncologists, methodologists, a pathologist and a radiologist, with particular expertise in the field of renal cancer care. Since 2015, the Panel has incorporated two patient advocates 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/renalcellcarcinoma/.

1.3 Available publications

A quick reference document (Pocket Guidelines) is available presenting the main findings of the RCC Guidelines. This is an abridged version which may require consultation together with the full text version. All documents can be accessed on the EAU website: http://uroweb.org/guideline/renal-cell-carcinoma/.

1.4 Publication history and summary of changes

1.4.1 Publication history

The EAU RCC Guidelines were first published in 2000. This 2024 RCC Guidelines document presents a limited update of the 2023 publication.

1.4.2 Summary of changes

All chapters of the 2024 RCC Guidelines have been updated, based on the 2023 version of the Guidelines. References have been added throughout the document. Other key changes incorporated in this publication includes:

- A new section 5.2.3 on other investigations and emerging technologies;
- An update of Table 5.1: Bosniak classification of renal cysts;
- New summary of evidence (SOE) and recommendations for prognostic factors using the Leibovich and VENUSS scoring models;
- A new section 7.1.3.2.8 on off-clamp vs on clamp partial nephrectomy as well as accompanying new SOE and recommendations in section 7.1.3.4;
- A new update in section 7.1.4.3.6 on stereotactic ablative radiotherapy;
- New SOE and recommendations for neoadjuvant therapy in section 7.2.5.5;
- A new section 7.4.2.4 on small molecule inhibitors, as well as new accompanying SOE and recommendation is section 7.4.2.5;
- Updates on the SOE and recommendations in section 7.4.4.1.2;
- Updates to both figure 7.1 and figure 7.2;
- New SOE in section 7.4.4.2.2 as well as in both SOE and recommendation table 7.4.4.2.1;
- A new section 7.4.4.2 on other rare tumours;
- New SOE and recommendation in section 8.3;
- A new section 8.4 on patient involvement including a recommendation table.

2. METHODS

2.1 Data identification

For the 2024 RCC 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 RCC Guidelines was performed. Databases searched included Medline, EMBASE, and the Cochrane Libraries, covering a time frame between May 24th, 2022 and May 1st, 2023. Databases covered included Medline, EMBASE, and the Cochrane Library. After de-duplication, a total of 1,901 unique records were identified, retrieved and screened for relevance. A search strategy is published online: https://uroweb.org/guidelines/renal-cell-carcinoma/publications-appendices.

Recommendation within the Guidelines are developed by the panels to prioritise clinically important care decisions. The strength of each recommendation is determined by the balance between desirable and undesirable consequences of alternative management strategies, the quality of the evidence (including certainty of estimates), and the nature and variability of patient values and preferences. This decision process, which can be reviewed in the strength rating forms which accompany each guideline statement, addresses a number of key elements:

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

Strong recommendations typically indicate a high degree of evidence quality and/or a favourable balance of benefit to harm and patient preference. Weak recommendations typically indicate availability of lower quality evidence, and/or equivocal balance between benefit and harm, and uncertainty or variability of patient preference [2].

Additional methodology information and a list of associations endorsing the EAU Guidelines can be found in the online: https://uroweb.org/eau-guidelines/methodology-policies.

2.2 Review

All publications ensuing from systematic reviews (SR)s have been peer reviewed. The 2021 print of the RCC Guidelines was peer-reviewed prior to publication.

2.3 Future goals

The RCC Guideline Panel supports the focus on patient-reported outcomes as well as the development of clinical quality indicators. A number of key quality indicators for this patient group have been selected:

- the proportion of patients undergoing thorax computed tomography (CT) for staging of pulmonary metastasis;
- proportion of patients with T1aN0M0 tumours undergoing nephron-sparing surgery (NSS) as first treatment;
- the proportion of patients with metastatic RCC (mRCC) offered systemic therapy;
- the proportion of patients who undergo minimally invasive or operative treatment as first treatment who die within 30 days.

The Panel have set up a database to investigate current practice in follow-up of RCC patients in a number of European centres. Assessing patterns of recurrence and use of imaging techniques are primary outcomes for this project.

In addition, the Panel will collect data from various European datasets on atypical recurrences following minimally invasive renal surgery to establish incidence and insight on potential causes, their management and outcome.

Further, a registry for Bosniak IV cysts with single nodularity will be established to investigate if diameter of the cyst or nodule is leading in clinical management.

The results of ongoing and new systematic reviews will be included in future updates of the RCC Guidelines:

- Systematic review of prevalence of intraperitoneal recurrences following robotic/laparoscopic partial nephrectomy;
- Systematic review of individual, unit and hospital surgical volume for radical and partial nephrectomy and their impact on outcomes;
- RECUR database analysis of recurrent disease/follow-up;
- Systematic review on management of oligometastatic and oligoprogressive disease.

3. EPIDEMIOLOGY, AETIOLOGY AND PATHOLOGY

3.1 Epidemiology

Renal cell carcinoma represents around 3% of all cancers, with the highest incidence occurring in Western countries [3, 4]. In 2020, there were an estimated 431,288 new cases of RCC globally, of which 138,611 in Europe [5]. The higher incidence in Europe and North America is hypothesized to be due to a higher prevalence of small renal masses (SRMs) in settings where abdominal imaging is more ubiquitous. In 2020, Lithuania reported the highest overall rate of RCC, followed by Czechia, with estimated age-standardised rates (ASRs) of 14.5/100,000 and 14.42/100,000, respectively. A person living in Czechia has a 2.83% risk of developing RCC [4, 5]. Generally, during the last two decades until recently, there has been an annual increase of about 2% in incidence both worldwide and in Europe. In 2022, worldwide mortality from RCC was 179,368 deaths (115,600 men and 63,768 women), with a calculated global ASR rate of 1.8/100,000 [5].

There has been a decrease in mortality 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 [3, 4].

Renal cell carcinoma is the most common solid lesion within the kidney and accounts for approximately 90% of all kidney malignancies. It comprises different RCC subtypes with specific histopathological and genetic characteristics. There is a 1.5–2.0:1 predominance in men over women with a higher incidence in the older population [4-6].

3.2 Aetiology

Established risk factors include lifestyle factors such as smoking (hazard ratio [HR]: 1.23–1.58), obesity BMI (> 35 vs. < 25), (HR: 1.71 [1.06-2.79]), hypertension (HR: 1.70 [1.30-2.22]) and metabolic syndrome (RR 1.62 [1.41-1.87]) [4-10]. 50.2% of patients with RCC are current or former smokers. By histology, the proportions of current or former smokers range from 38% in patients with chromophobe carcinoma (chRCC) to 61.9% in those with collecting duct/medullary carcinoma [11]. In a SR, diabetes was also found to be detrimental [12]. Having a first-degree relative with kidney cancer is also associated with an increased risk of RCC [13]. Moderate alcohol consumption appears to have a protective effect for reasons as yet unknown, while any physical activity level also seems to have some protective effect [4, 5, 12, 14, 15]. A number of other factors have been suggested to be associated with higher or lower risk of RCC, including specific dietary habits and occupational exposure to specific carcinogens, but no high-quality evidence level exists [6, 16]. The most effective prophylaxis is to avoid cigarette smoking and reduce obesity [4-7]. Genetic risk factors are known to play a role in the development of RCC (see Section 3.5.6 - Hereditary kidney tumours).

3.3 Screening

Despite a growing interest from both patients and clinicians in RCC screening programmes, there is a relative lack of studies reporting the efficacy, cost-effectiveness, and optimal modality for RCC screening. Urinary dipstick is an inadequate screening tool due to low sensitivity and specificity. Also incidence of RCC with non-visible haematuria is low; 0.58% [17]. No clinically validated urinary or serum biomarkers have as yet been identified. Computed tomography cannot be recommended due to cost, radiation dose and the increased potential for other incidental findings. Ultrasound (US) could be used and has acceptable sensitivity and specificity, although it is tumour size and operator dependant. Major barriers to population screening include the relatively low prevalence of the disease, the potential for false positives and over-diagnosis of slow-growing kidney tumours. Targeting high-risk individuals and/or combining detection of RCC with other routine health screenings may represent pragmatic options to improve the cost-effectiveness and reduce the potential harms of RCC screening [18-20]. Targeting of high-risk patient groups e.g., those with end-stage renal disease (ESRD) which is associated with a 10-fold increased risk of developing RCC may also be a valid approach (see Section

3.5.2) [21]. There is currently no evidence to support primary screening in the general population.

3.3.1 Summary of evidence and recommendations for epidemiology, aetiology and screening

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
There is no evidence to support primary screening for RCC.	4

Recommendations	Strength rating
Increase physical activity, eliminate cigarette smoking and in obese patients reduce weight are the primary preventative measures to decrease risk of RCC.	Strong
Do not routinely screen any population for primary RCC.	Weak

3.4 Histological diagnosis

Renal cell carcinomas and other renal tumours comprise a broad spectrum of histopathological entities described in the 5th edition of the World Health Organization (WHO) classification of urogenital tumours published in 2022 [22-24]. The 5th edition presents standard morphologic diagnostic criteria, combined with immunohistochemistry and relevant molecular tests was significantly revised as compared to the 2016 classification [25]. The global application of next-generation sequencing (NGS) will result in a diagnostic shift from morphology to molecular analyses. Therefore, a molecular-driven renal tumour classification has been introduced in addition to morphology-based renal tumours (Table 3.1). Examples of molecularly-defined epithelial renal tumours include SMARCB1-deficient renal medullary carcinoma, TFE3- and TFEB-rearranged RCC, ALK-rearranged RCC, and elongin C (ELOC)-mutated RCC. The most profound changes in the 2022 WHO classification mainly relate to rare kidney tumours.

There are three main RCC types: clear cell (ccRCC), papillary (pRCC no longer divided into type I and II) and chRCC. The RCC type classification has been confirmed by cytogenetic and genetic analyses [25, 26] (LE: 2b). The 5-year overall survival (OS) for non-metastatic (including N0-N1) chromophobe, papillary, clear-cell and collecting duct RCC is 91%, 82%, 81% and 44%, respectively [27]. Sarcomatoid RCC is not a specific subtype, but essentially represents a pattern of de-differentiation associated with adverse outcome and poor cancer-specific survival (CSS), irrespective of the underlying RCC subtype; it should be graded as WHO/ISUP (International Society of Urological Pathology) grade IV. Multilocular cystic renal neoplasm of low malignant potential is a new subtype of cRCC in the 2022 classification. A new group "oncocytic and chromophobe tumours" encompass oncocytoma together with chRCC and other oncocytic tumours. Other oncocytic tumours include tumours that do not strictly fit into either the oncocytoma or chRCC subtypes [22, 28].

Histological diagnosis includes, besides RCC type; evaluation of ISUP nuclear grade, sarcomatoid features, vascular invasion, tumour necrosis, and invasion of the collecting system and peri-renal fat, pT, or even pN categories. The four-tiered WHO/ISUP grading system has replaced the Fuhrman grading system [22, 25].

Table 3.1 World Health Organization classification of renal tumours 2022 [22, 23]

WHO classification of renal tumours 2022	
1. Renal Cell Tumours	
01.I	Clear cell renal tumours
	Clear cell RCC
	Multilocular cystic renal neoplasm of low malignant potential
01.II	Papillary renal tumours
	Papillary adenoma
	Papillary RCC
01.III	Oncocytic and chromophobe renal tumours
	Oncocytoma of the kidney
	Chromophobe RCC
	Other oncocytic tumours of the kidney
01.IV	Collecting duct tumours

	Collecting duct carcinoma
01.V	Other renal tumours
	Clear cell papillary renal cell tumour
	Mucinous tubular and spindle cell carcinoma
	Tubulocystic RCC
	Acquired cystic disease-associated RCC
	Eosinophilic solid and cystic (ESC) RCC
	RCC NOS (Not Otherwise Specified)
01.VI	Molecularly defined renal tumours
	TFE3-rearranged RCCs
	TFEB-altered RCC (*TFEB*-rearranged RCC and *TFEB* amplified RCC)
	ELOC (formerly *TCEB1*)-mutated RCC
	Fumarate hydratase-deficient RCC
	Succinate dehydrogenase-deficient RCC
	ALK-rearranged RCCs
	SMARCB1-deficient renal medullary carcinoma
2. Metanephric tumours	
	Metanephric adenoma
	Metanephric adenofibroma
	Metanephric stromal tumour
3. Mixed epithelial and stromal tumour family	
	Mixed epithelial and stromal tumour
	Adult cystic nephroma
4. Renal mesenchymal tumours	
04.I	Adult renal mesenchymal tumours
	Classic angiomyolipoma/PEComa of the kidney
	Epitheloid angiomyolipoma/epithelioid PEComa of the kidney
	Renal haemangioblastoma
	Juxtaglomerular cell tumour
	Renomedullary interstitial cell tumour
04.II	Paediatric renal mesenchymal tumours
	Ossifying renal tumour of infancy
	Congenial mesoblastic nephroma
	Rhabdoid tumour of kidney
	Clear cell sarcoma of kidney
5. Embryonal neoplasms of the kidney	
Nephroblastic tumours	
	Nephrogenic rests
	Pediatric cystic nephroma
	Cystic partially differentiated nephroblastoma
	Nephroblastoma
6. Miscellaneous tumours	
Germ cell tumours of the kidney	

3.4.1 ***Clear-cell RCC***

Overall, ccRCC representing about 70% of RCC [23], is well circumscribed with a pseudocapsule. The cut surface is golden-yellow, often with haemorrhage and necrosis. Loss of chromosome 3p and mutation of the von Hippel-Lindau (VHL) gene at chromosome 3p25 are frequently found. The loss of von Hippel-Lindau protein function

contributes to tumour initiation, progression, and metastases. The 3p locus harbours additional ccRCC tumour suppressor genes (*UTX, JARID1C, SETD2, PBRM1, BAP1*) [22]. For details about prognosis, see Section 6.3.

3.4.1.1 Multilocular cystic renal neoplasm of low malignant potential (MCNLMP)

Indolent, exclusively cystic, multiloculated renal tumour devoid of any expansile solid growth, with clear cells lining and low grade nuclei. Detection of small solid expansive nodules and tumour necrosis are incompatible with MCNLMP. It represents 0.5-2.5% of all renal tumours and is a benign lesion. There are no reports of progression, metastases or cancer-related death with long-term follow-up [22, 23].

*3.4.2 **Papillary RCC***

Papillary RCC (pRCC) is the second-most encountered morphotype of RCC accounting for 13-20% of renal epithelial tumours. It is usually circumscribed and characterised by papillary or tubulopapillary architecture, without specific features of other RCCs with papillary architecture [22, 23]. Papillary RCC has traditionally been subdivided into two types; Type I and II pRCC [25]. However, in the new 2022 WHO classification, the former pRCC type I is now referred to as "pRCC of classic pattern". Three additional morphologic patterns of pRCC have been introduced including: a) bi-phasic (alveolo-squamoid) pattern exhibiting mostly solid growth; b) papillary neoplasm with reverse nuclear polarity, previously described as "oncocytic low-grade pRCC"; and c) Warthin-like pRCC that exhibits brisk inflammation mimicking Warthin tumour of the salivary gland.

Genetic changes of pRCC include trisomies and tetrasomies of chromosomes 7 and 17 and loss of Y-chromosome. Mesenchymal-epithelial Transition (MET) gene mutations are more frequent in low-grade pRCC.

The typical histology of classical pattern pRCC, formally type I pRCC, (narrow papillae without any binding, and only microcapillaries in papillae) explains its typical clinical signs. Narrow papillae without any binding and a tough pseudo-capsule explain the ideal rounded shape (Pascal's law) and fragility (specimens have a "minced meat" structure). Tumour growth causes necrotisation of papillae, which is a source of hyperosmotic proteins that cause subsequent "growth" of the tumour, fluid inside the tumour, and only a serpiginous, contrast-enhancing margin. Stagnation in the microcapillaries explains the minimal post-contrast attenuation on CT. Classical pattern pRCC can imitate a pathologically changed cyst (Bosniak IIF or III). The typical signs of classical pattern pRCC are an ochre colour, frequently exophytic, extra-renal growth and low grade. A risk of renal tumour biopsy tract seeding exists (12.5%), probably due to the fragility of the tumour papillae [29].

*3.4.3 **Chromophobe RCC***

Chromophobe RCC is now grouped in "Oncocytic and chromophobe tumours". Most chRCCs are discovered incidentally in asymptomatic patients [22, 23]. Overall, chRCC presents as a pale tan, relatively homogenous and tough, well-demarcated mass without a capsule. Most tumours are sporadic. Rare hereditary forms include Birt-Hogg-Dubé (BHD) syndrome with mutations in folliculin and Cowden syndrome with mutations in PTEN see Section 3.5.6 for further information [22, 23]. Chromophobe RCC cannot be graded by the WHO/ISUP (formerly Fuhrman) grading system because of its innate nuclear atypia. An alternative grading system has been proposed, but has yet to be validated [22, 23]. Loss of chromosomes-Y, 1, 2, 6, 10, 13, 17 and 21 are typical genetic changes [22, 23]. The prognosis is relatively good, with high 5-year recurrence-free survival (RFS), and 10-year CSS. The five- and 10-year RFS rates were 94.3% and 89.2%, respectively. Recurrent disease developed in 5.7% of patients, and 76.5% presented with distant metastases with 54% of metastatic disease diagnoses involving a single organ, most commonly bone. Recurrence and death after surgically resected chRCC are rare. For completely excised lesions < pT2a without coagulative necrosis or sarcomatoid features, the prognosis is excellent [30].

3.5 Other renal tumours

Other renal tumours constitute the remaining renal cortical tumours. These include a variety of uncommon, sporadic, and familial carcinomas/tumours, some only recently described, as well as a group of unclassified carcinomas. A summary of these tumours is provided in Table 3.1, but some clinically relevant tumours and extremely rare entities are mentioned below. About 15% of excised renal masses are benign [31].

*3.5.1 **Renal medullary carcinoma (SMARCB1-deficient renal medullary carcinoma)***

Renal medullary carcinoma (RMC) (referred to as SMARCB1-deficient renal medullary carcinoma in the 2022 WHO Classification) is a very rare tumour, comprising < 0.5% of all RCCs [32], predominantly diagnosed in young adults of African ancestry (median age 28 years) with sickle haemoglobinopathies (including sickle cell trait). It has a male predominance of 2:1 and is mainly centrally located with ill-defined borders. Renal medullary carcinoma is one of the most aggressive RCCs [33, 34] and most patients (~67%) will present with metastatic disease [33, 35]. Even patients who present with seemingly localised disease may develop unequivocal

metastases shortly (within weeks) after diagnosis (for treatment see Chapter 7). Apart from the RMC described above, some patients present with identical tumours without haemoglobinopathy. Such tumours have been described as "unclassified RCC with medullary phenotype" [22].

3.5.2 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 ESRD. Renal cell carcinomas of native end-stage kidneys are found in approximately 4% of patients with ESRD. Their lifetime risk of developing RCCs is at least ten times higher than in the general population. Compared with sporadic RCCs, RCCs associated with ESRD are generally multicentric and bilateral, found in younger patients (mostly male), and are less aggressive. Whether the relatively indolent outcome of tumours in ESRD is due to the mode of diagnosis or a specific ACKD-related molecular pathway still has to be determined. Although the histological spectrum of ESRD tumours is like that of sporadic RCC; pRCC occur relatively more frequently [28, 36]. A specific subtype of RCC occurring only in end-stage kidneys has been described as "acquired cystic disease-associated RCC" (ACD-RCC). Tumours present exclusively in patients with ACKD, usually after long-term dialysis. The vast majority occur in men. Tumours are often multiple and bilateral and, in most cases, have an indolent clinical behaviour; although, aggressive courses have been documented [22].

3.5.3 Papillary adenoma

These tumours have a papillary or tubular architecture of low nuclear grade and may be up to 15 mm in diameter, or smaller, according to the 2022 WHO classification [22].

3.5.4 Renal oncocytoma

Oncocytoma is a benign tumour representing 4-7% of all solid renal tumours and 30% of benign surgically removed kidney masses are contributed to oncocytoma [25, 37]. The diagnostic accuracy of imaging modalities (CT, magnetic resonance imaging [MRI]) in renal oncocytoma is limited and histopathology remains the only reliable diagnostic modality [25, 37]. However, ^{99m}Tc-sestamibi (SestaMIBI, MIBI) SPECT/CT has shown promising initial results for the differentiation between benign and low-grade RCC [38-41]. Standard treatment for renal oncocytoma is similar to that of other renal tumours; surgical excision by partial- or radical nephrectomy (RN) with subsequent histopathological verification. However, due to the inability of modern imaging techniques to differentiate benign from malignant renal masses, there is a renewed interest in renal mass biopsy (RMB) prior to surgical intervention. Accuracy of the biopsy and management of advanced/progressing oncocytomas need to be considered in this context since oncocytic renal neoplasms diagnosed by RMB at histological examination after surgery showed oncocytoma in only 64.6% of cases. The remainder of the tumours were mainly chRCC (18.7% including 6.3% hybrid oncocytic/chromophobe tumours which have now been grouped histologically with chRCC) [22, 23], other RCCs (12.5%), and other benign lesions (4.2%) [42, 43]. The 2022 WHO classification strictly excludes that a definitive diagnosis of oncocytoma be done on a needle-core biopsy. The majority of oncocytomas slowly progress in size with an annual growth rate of approximately 2 mm [37]. Preliminary data show that active surveilnace (AS) may be a safe option to manage oncocytoma in appropriately selected patients. Potential triggers to change management of patients on AS are not well defined [44, 45].

3.5.5 Other oncocytic tumours of the kidney

Other oncocytic tumours of the kidney are a heterogeneous group of oncocytic tumours not classifiable as oncocytoma, chRCC, or other tumour types with eosinophilic features. These tumours are typically indolent, so it is important to distinguish such low-grade tumours from the high-grade unclassified RCCs that typically behave aggressively. In the setting of Birt–Hogg–Dubé syndrome (see Section 3.5.6), tumours with such intermediate features (hybrid oncocytic tumours) also exist, typically being multifocal and bilateral. As this is a heterogeneous tumour group, it is likely that new subtypes of renal neoplasia will emerge. There are already two emerging entities: eosinophilic vacuolated tumour (EVT) and low-grade oncocytic tumour (LOT) [22].

3.5.6 Hereditary kidney tumours

Five to eight percent of RCCs are hereditary; to date there are ten hereditary RCC syndromes associated with specific germline mutations, RCC histology, and comorbidities. Hereditary RCC syndromes are often suggested by family history, age of onset and presence of other lesions typical for the respective syndromes. Median age for hereditary RCC is 37 years; 70% of hereditary RCC tumours are found in the lowest decile (age 46 years or younger) of all RCC tumours [46]. Hereditary kidney tumours are found in the following entities: VHL syndrome; hereditary pRCC; Birt-Hogg-Dubé syndrome; Fumarate hydratase-deficient RCC (FHD-RCC), previously called hereditary leiomyomatosis and RCC (HLRCC); tuberous sclerosis; germline succinate dehydrogenase (SDH) mutation; non-polyposis colorectal cancer syndrome; hyperparathyroidism-jaw tumour syndrome; phosphatase and tensin homolog (PTEN) hamartoma syndrome (PHTS); constitutional chromosome 3 translocation; familial

non-syndromic ccRCC and BAP1-associated RCC [47]. Renal medullary carcinoma can be included because of its association with hereditary haemoglobinopathies [48-51].

Patients with hereditary kidney cancer syndromes may require repeated surgical intervention [52, 53]. In most hereditary RCCs nephron-sparing approaches are recommended. The exceptions are FHD-RCC and SDH syndromes for which immediate surgical intervention is recommended due to the aggressive nature of these tumours. For other hereditary syndromes such as VHL, surveillance is recommended until the largest tumour reaches 3 cm in diameter; this to limit the number of repeat interventions [54, 55]. Active surveillance for VHL, SDH and FHD-RCC should, in individual patients, follow the size, growth rate and location of the tumours, rather than applying a standardised follow-up interval. Regular screening for both renal and extra-renal lesions should follow international guidelines for these syndromes [55]. Multidisciplinary and co-ordinated care should be offered, where appropriate [56]. In FHD-RCC, renal screening in relatives has shown benefit in detecting early-stage RCCs [57], with HLRCCs appearing to have unique molecular profiles.

Although not hereditary, somatic fusion translocations of *TFE3* and *TFEB* may affect 15% of patients with RCC younger than 45 years and 20-45% of children and young adults diagnosed with RCC [58].

A phase II trial demonstrated clinical activity of an oral HIF-2α (hypoxia-inducible factor) inhibitor MK-6482 (belzutifan) in VHL patients [59]. Additional information on treatment of VHL can be found in Section 7.4.4.

*3.5.7 **Classical Angiomyolipoma***

Classical angiomyolipoma (AML)/PEComa of the kidney is a benign mesenchymal tumour, which can occur sporadically or as part of tuberous sclerosis complex [60]. Overall prevalence is 0.44%, with 0.6% in female and 0.3% in male populations. Only 5% of these patients present with multiple AMLs [61]. Angiomyolipoma belongs to a family of so-called PEComas (perivascular epithelioid cell tumours), characterised by the proliferation of perivascular epithelioid cells. Some PEComas can behave aggressively and even metastasise, while classic AMLs are completely benign [25, 48, 62]. Ultrasound, CT, and MRI often lead to the diagnosis of AMLs due to the presence of adipose tissue; however, in fat-poor AML, diagnostic imaging cannot reliably identify these lesions. Percutaneous biopsy is rarely useful. Renal tumours that cannot be clearly identified as benign during the initial diagnostic work-up should be treated according to the recommendations provided for the treatment of RCC. In tuberous sclerosis, AML can be found in enlarged lymph nodes (LNs), which does not represent metastatic spread but a multicentric spread of AMLs. In rare cases, an extension of a non-malignant thrombus into the renal vein or inferior vena cava (IVC) can be found, associated with an angiotrophic-type growth of AML. Epithelioid AML, a very rare variant of AML, consists of at least 80% epithelioid cells and with mean age of onset of 50 years (range 30-80 years), without gender predilection [48, 62]. Epithelioid AMLs are potentially malignant with a variable proportion of cases with aggressive behaviour [63]. Criteria to predict the biological behaviour in epithelioid AML were proposed by the WHO 2022 [22, 23]. Angiomyolipoma, in general, has a slow and consistent growth rate, and minimal morbidity [64]. Subtypes of AML are oncocytic AML and AML with epithelial cysts [22].

In some cases, larger AMLs can cause local pain. The main complication of AMLs is spontaneous bleeding in the retroperitoneum or into the collecting system, which can be life threatening. Bleeding is caused by spontaneous rupture of the tumour. Little is known about the risk factors for bleeding, but it is believed to increase with tumour size and may be related to the angiogenic component of the tumour that includes irregular blood vessels [64]. The major risk factors for bleeding are tumour size, grade of the angiogenic component, and the presence of tuberous sclerosis.

3.5.7.1 Treatment of angiomyolipoma

Active surveillance is the most appropriate option for most AMLs (48%). In a group of patients on AS, only 11% of AMLs showed growth, and spontaneous bleeding was reported in 2%, resulting in active treatment in 5% of patients [64] (LE: 3). The association between AML size and the risk of bleeding remains unclear and the traditionally used 4-cm cut-off should not per se trigger active treatment [64]. When surgery is indicated, NSS is the preferred option, if technically feasible. Main disadvantages of less invasive selective arterial embolisation (SAE) are more recurrences and a need for secondary treatment (0.85% for surgery vs. 31% for SAE). For thermal ablation only limited data are available, and this option is used less frequently [64].

Active treatment (SAE, surgery or ablation) should be instigated in case of persistent pain, ruptured AML (acute or repeated bleeding) or in case of a very large AML. Specific patient circumstances may influence the choice to offer active treatment, such as patients at high risk of abdominal trauma, females of childbearing age or patients in whom follow-up or access to emergency care may be inadequate. Selective arterial embolisation is an option in case of life-threatening AML bleeding.

In patients diagnosed with tuberous sclerosis, size reduction of often bilateral AMLs can be induced by inhibiting the mTOR pathway using everolimus, as demonstrated in RCTs [65, 66]. In a small phase II trial

(n = 20), efficacy of everolimus was demonstrated in sporadic AML as well. A 25% or greater reduction in tumour volume at four and six months was demonstrated in 55.6% and 71.4% of patients, respectively. However, 20% of patients were withdrawn due to toxicities and 40% self-withdrew from the study due to side effects [67].

Table 3.2: Other renal cortical tumours and recommendations for treatment (strength rating: weak)

Entity	Clinical relevant notes	Malignant potential	Treatment
Collecting duct carcinoma	Formerly bellini duct carcinoma. No hemoglobinopathy or *SMARCB1* abnormality. Rare, often presenting at an advanced stage (N+ 44% and M1, 33% at diagnosis). The HR CSS in comparison with ccRCC is 4.49 [22, 23, 68].	High, very aggressive. Median survival 30 months [69].	Surgery. Systemic therapy and surgery in metastatic disease [70].
Clear-cell papillary renal cell tumour	Patient with ACKD, 100 times greater risk compared with general population [23].	Indolent	Surgery, NSS, discuss active surveilance.
Mucinous tubular and spindle cell carcinoma	Tumour is associated with the loop of Henle. < 1% of renal neoplasm. Female predilection (3–4:1) [23].	Intermediate	Surgery, NSS.
Tubulocystic RCC	Rare (< 1%). Mainly men, imaging can be Bosniak III or IV.	Low (90% indolent)	Surgery, NSS.
Eosinophilic solid and cystic RCC (ESC RCC)	Usually alteration of TCS genes. Predominantly in adult women. Some with TSC (tuberous sclerosis complex) syndrome.	Rarely metastatic.	NSS.
TFE3 re-arranged RCC	Gene fusions involving *TFE3* with one of many different partner genes. Formerly translocation RCC (TRCC) Xp11.2. Appr. 40 % of paediatric RCC and 1.6–4% of adult RCC [24].	Survival similar to clear cell RCC	Surgery. Systemic therapy in metastatic disease.
TFEB altered (re-arranged and amplified) RCC	Gene fusions involving the *TFEB* transcription factor, typically via a t(6;11)(p21;q12) translocation resulting in a *MALAT1-TFEB* gene fusion. Formerly translocation RCC t(6;11). Less common than *TFE3*-re-arranged RCC. Appr. 100 cases in the literature [23]. *TFEB*-amplified in older patient and has a worse prognosis.	More indolent than the TFE3-rearranged RCC, with fewer than 10% of cases resulting in patient death.	Surgery. Systemic therapy in metastatic.
ELOC (formerly *TCBE1*)-mutated RCC	Twenty cases described in literature. Typically T1.	Indolent. Only 2 metastatic cases described.	NSS.
Fumarate hydratase-deficient RCC	Formerly hereditary leiomyomatosis and RCC-associated RCC. Alterations in the *FH* gene. Autosomal dominant. 21–30% lifetime risk of RCC [57]. Cutanous leiomyomas, female uterine leiomyoma or leiomyosarcoma. More common in males. Median age 44 years [22, 28, 71].	Often aggressive.	Immediate surgery. No data about treatment of metastatic disease. Genetic counselling in the family. Imaging screening in relatives [57].

Succinate dehydrogenase-deficient RCC (SDH-deficient RCC)	Rare. 0.05–0.2 % of all RCCs.	A metastatic rate of 11%	Surgery, NSS. Long-term follow-up and surveillance for other SDH-deficient neoplasms (i.e. paraganglioma, SDH-deficient gastrointestinal stromal tumour, and pituitary adenoma) is indicated for cases associated with germline mutation [23].
ALK-rearranged RCC	Gene fusions involving anaplastic lymphoma kinase gene (ALK) at chromosome *2p23*. Appr. 40 cases described.	Low (90% indolent)	Surgery, NSS.
Metanephric tumours	Divided into metanephric adenoma, adenofibroma, and metanephric stromal tumours.	Benign	NSS.
Mixed epithelial and stromal renal tumour	It encompasses 2 benign leasions - mixed epithelial and stromal tumour of the kidney (MEST) and adult cystic nephroma. Imaging – Bosniak type III or IIF/IV. Overwhelmingly in women (7:1).	Benign	Active surveillance. NSS.
Renal cysts/cystic lesions	Simple cysts are frequently occurring, while occurring septa, calcifications and solid components require follow-up and/or management.	Mostly benign	Treatment or follow-up recommendation based on Bosniak classification.

3.5.8 ***Cystic renal tumours***

Cystic renal lesions are classified according to the Bosniak classification (see Section 5.2.5). Bosniak I and II cysts are benign lesions which do not require follow-up [72]. Bosniak IV cysts are mostly (83%) malignant tumours with pseudo-cystic changes only [73]. Bosniak IIF and III cysts remain challenging for clinicians. The differentiation of benign and malignant tumour in categories IIF/III is based on imaging, mostly CT, with an increasing role of MRI and contrast-enhanced US (CEUS). Computed tomography shows poor sensitivity (36%) and specificity (76%; κ [kappa coefficient] = 0.11) compared with 71% sensitivity and 91% specificity (κ = 0.64) for MRI and 100% sensitivity and 97% specificity for CEUS (κ = 0.95) [74]. Surgical and radiological cohorts pooled estimates show a prevalence of malignancy of 0.51 (0.44-0.58) in Bosniak III and 0.89 (0.83-0.92) in Bosniak IV cysts, respectively. In a SR, less than 1% of stable Bosniak IIF cysts showed malignancy during follow-up. Twelve percent of Bosniak IIF cysts had to be reclassified to Bosniak III/IV during radiological follow-up, with 85% of these showing malignancy, which is comparable to the malignancy rates of Bosniak IV cysts [72]. The updated Bosniak classification strengthens the classification and includes also MRI [75] and even CEUS diagnostic criteria [76].

The most common histological types for Bosniak III cysts is ccRCC with pseudo-cystic changes and low malignant potential [77, 78]; multilocular cystic renal neoplasm of low malignant potential, see Section 3.4.1.1; classical pattern pRCC (very low malignant potential); benign multilocular cyst; benign group of mixed epithelial and stromal renal tumour (mixed epithelial and stromal tumour of the kidney and adult cystic nephroma); and other rare entities. Surgery in Bosniak III cysts will result in over-treatment in 49% of the tumours which are lesions with a low malignant potential. In view of the excellent outcome of these patients in general, a surveillance approach is an alternative to surgical treatment [72, 75, 79, 80].

3.6 Summary of evidence and recommendations for the management of other renal tumours

Summary of evidence	LE
A variety of renal tumours exist of which approximately 15% are benign .	3
The most common renal tumours are three malignant types of RCC (clear cell, papillary and chromophobe) and two benign renal tumours: oncocytoma and angiomyolipoma.	3
A definitive histopathological diagnosis of oncocytoma cannot be made on a needle-core biopsy, because chRCC can show intratumoural heterogeneity with areas very similar to oncocytoma.	3
Histological work up and results of AS of Bosniak III cysts shows low risk of malignant potential/ course.	2

Recommendations	Strength rating
Manage Bosniak type III cysts the same as localised RCC, or offer active surveillance (AS).	Weak
Manage Bosniak type IV cysts the same as localised RCC.	Strong
Offer AS to patients with biopsy-proven oncocytoma or other oncocytic renal tumours as an acceptable alternative to surgery or ablation.	Weak
Treat angiomyolipoma (AML) with selective arterial embolisation or nephron-sparing surgery, in: • large tumours (a recommended threshold of intervention does not exist); • females of childbearing age; • patients in whom follow-up or access to emergency care may be inadequate; • persistent pain or acute or repeated bleeding episodes.	Weak
Offer systemic therapy (everolimus) to patients at need for therapy with surgically unresectable AMLs not amendable to embolisation.	Weak

4. STAGING AND CLASSIFICATION SYSTEMS

4.1 Staging

The Tumour Node Metastasis (TNM) classification system is recommended for clinical and scientific use [81]. A supplement was published in 2012, and the latter's prognostic value was confirmed in single- and multi-institution studies [82, 83]. Tumour size, venous invasion, renal capsular invasion, adrenal involvement, 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 [84];
- The value of size stratification of T2 tumours has been questioned [85];
- Renal sinus fat invasion might carry a worse prognosis than perinephric fat invasion, but, is nevertheless included in the same pT3a stage group [86-89] (LE: 3);
- Sub T-stages (pT2b, pT3a, pT3c and pT4) may overlap [83];
- For adequate M staging, accurate pre-operative imaging (chest and abdominal CT) should be performed [90, 91] (LE: 4).

A proposed imaging analysis of Tumor Contour Irregularity might be a valuable tool to enhance the preoperative staging between T1 and T3a RCCs for treatment decisions [92].

The TNM classification should not be considered the only criterion for clinical decision-making, but patient's condition, comorbidities and wishes are of fundamental importance to select the most optimal treatment. A clinically-guided RCC staging classification was proposed in 2022 by the EAU Panel, based on changes observed in the management of SRM, locally advanced and metastatic disease [84].

Table 4.1: 2017 TNM classification system [93]

T - Primary tumour				
TX	Primary tumour cannot be assessed			
T0	No evidence of primary tumour			
T1	Tumour ≤ 7 cm or less in greatest dimension, limited to the kidney			
	T1a	Tumour ≤ 4 cm or less		
	T1b	Tumour > 4 cm but ≤ 7 cm		
T2	Tumour > 7 cm in greatest dimension, limited to the kidney			
	T2a	Tumour > 7 cm but ≤ 10 cm		
	T2b	Tumours > 10 cm, limited to the kidney		
T3	Tumour extends into major veins or perinephric tissues but not into the ipsilateral adrenal gland and not beyond Gerota fascia			
	T3a	Tumour extends into the renal vein or its segmental branches, or invades the pelvicalyceal system or invades perirenal and/or renal sinus fat*, but not beyond Gerota fascia*		
	T3b	Tumour grossly extends into the vena cava below diaphragm		
	T3c	Tumour grossly extends into vena cava above the diaphragm or invades the wall of the vena cava		
T4	Tumour invades beyond Gerota fascia (including contiguous extension into the ipsilateral adrenal gland)			
N - Regional Lymph Nodes				
NX	Regional lymph nodes cannot be assessed			
N0	No regional lymph node metastasis			
N1	Metastasis in regional lymph node(s)			
M - Distant metastasis				
M0	No distant metastasis			
M1	Distant metastasis			
pTNM stage grouping				
Stage I	T1	N0	M0	
Stage II	T2	N0	M0	
Stage III	T3	N0	M0	
	T1, T2, T3	N1	M0	
Stage IV	T4	Any N	M0	
	Any T	Any N	M1	

A help desk for specific questions about TNM classification is available at http://www.uicc.org/tnm.
**Adapted based on the American Joint Committee on Cancer (AJCC), 8th Edn. 2017 [94].*

4.2 Anatomic classification systems

Objective anatomic classification systems, such as the Preoperative Aspects and Dimensions Used for an Anatomical (PADUA) classification system, the R.E.N.A.L. nephrometry score, the C-index, an Arterial Based Complexity (ABC) Scoring System and Zonal NePhRO scoring system, have been proposed to standardise the description of renal tumours [95-97]. These systems include assessment of tumour size, exophytic/endophytic properties, proximity to the collecting system and renal sinus, and anterior/posterior or lower/upper pole location.

The use of such a system is helpful as it allows objective prediction of potential morbidity of NSS and tumour ablation techniques. These tools provide information for treatment planning, patient counselling, and comparison of PN and tumour ablation series. However, when selecting the most optimal treatment option, anatomic scores must 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. The majority of RCCs are detected incidentally by non-invasive imaging investigating various non-specific symptoms and other abdominal diseases [98] (LE: 3). In a prospective observational cohort study, 60% of patients overall, 87% of patients with stage 1a renal tumours and 36% of patients with stage III or IV disease presented incidentally [99]. The classic triad of flank pain, visible haematuria, and palpable abdominal mass is rare (6-10%) and correlates with aggressive histology, advanced disease, and poorer outcomes [99-101] (LE: 3). Paraneoplastic syndromes are found in approximately 30% of patients with symptomatic RCCs [102] (LE: 4). Some symptomatic patients present with symptoms caused by metastatic disease, such as bone pain or persistent cough [103] (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 [104], 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 [105, 106] (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 [98] (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 [107] (LE: 3). Traditionally, US, CT and MRI are used for detecting and characterising renal masses. Most renal masses are diagnosed accurately by imaging alone.

*5.2.2 **Computed tomography or magnetic resonance imaging***

Computed tomography or MRI are used to characterise renal masses. Imaging must be performed unenhanced, in an early arterial phase, and in a parenchymal phase with intravenous contrast material to demonstrate enhancement. In CT imaging, enhancement in renal masses is determined by comparing Hounsfield units (HU) before, and after, contrast administration. A change of fifteen HU, or more, in the solid tumour parts demonstrates enhancement and thus vital tumour parts [108] (LE: 3). Computed tomography or MRI allows accurate diagnosis of RCC but cannot reliably distinguish oncocytoma and fat-free AML from malignant renal neoplasms [109-112] (LE: 3). Abdominal CT provides information on [113]:

- function and morphology of the contralateral kidney [114] (LE: 3);
- primary tumour extension;
- venous involvement;
- enlargement of locoregional LNs;
- condition of the adrenal glands and other solid organs (LE: 3).

Abdominal contrast-enhanced CT angiography is useful in selected cases when detailed information on the renal vascular supply is needed [115, 116]. If the results of CT are indeterminate, CEUS is a valuable alternative to further characterise renal lesions [117-120] (LE: 1b).

Magnetic resonance imaging may provide additional information on venous involvement if the extent of an IVC tumour thrombus is poorly defined on CT [121-124] (LE: 3). In MRI, especially high-resolution T2-weighted images provide a superior delineation of the uppermost tumour thrombus, as the inflow of the enhanced blood may be reduced due to extensive occlusive tumour thrombus growth in the IVC. The T2-weighted image with its intrinsic contrast allows a good delineation [124].

Magnetic resonance imaging is indicated in patients who are allergic to intravenous CT contrast medium and in pregnancy without renal failure [124, 125] (LE: 3). Magnetic resonance imaging allows the evaluation of a dynamic enhancement without radiation exposure. Advanced MRI techniques such as diffusion-weighted (DWI) and perfusion-weighted imaging are being explored for renal mass assessment [126]. Recently, the use of multiparametric MRI (mpMRI) to diagnose ccRCC via a clear cell likelihood score (ccLS) in SRMs was reported [127]. The ccLS is a 5-tier classification that denotes the likelihood of a mass representing ccRCC, ranging from 'very unlikely' to 'very likely'. The authors prospectively validated the diagnostic performance of ccLS in 57 patients with cT1a tumours and found a high diagnostic accuracy. The diagnostic performance of mpMRI-based ccLS was further validated in a larger retrospective cohort (n = 434) across all tumour sizes and stages [128], and ccLS was found to be an independent prognostic factor for identifying ccRCC.

For the diagnosis of complex renal cysts (Bosniak IIF–III) MRI may be preferable. The accuracy of CT is limited in these cases, with poor sensitivity (36%) and specificity (76%; κ = 0.11); MRI, due to a higher sensitivity for enhancement, showed a 71% sensitivity and 91% specificity (κ = 0.64). Contrast-enhanced US showed high sensitivity (100%) and specificity (97%), with a negative predictive value of 100% (κ = 0.95) [74].

In younger patients who are worried about the radiation exposure of frequent CT scans, MRI may be offered as alternative although only limited data exist correlating diagnostic radiation exposure to the development of secondary cancers [129].

A SR and meta-analysis [130] compared the diagnostic performance of CEUS vs. contrast-enhanced CT (CECT) and contrast-enhanced MRI (CEMRI) in the assessment of benign and malignant cystic and solid renal masses. Sixteen studies were included in the pooled analysis. The results suggested comparable diagnostic performance of CEUS compared with CECT (pooled sensitivity 0.96 [95% CI: 0.94-0.98], vs. 0.90 [95% CI: 0.86-0.93], for studies with a final diagnosis of benign or malignant renal masses by pathology), and CEUS vs. CEMRI (pooled sensitivity 0.98 [95% CI: 0.94-1.0], vs. 0.78 [95% CI: 0.66-0.91], for studies with final diagnosis by pathology report or reaffirmed diagnosis by follow-up imaging without pathology report). However, there were significant limitations in the data, including very few studies for CEMRI, clinical and statistical heterogeneity and inconsistency, and high risks of confounding.

*5.2.3 **Other investigations and emerging technologies***

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 [105, 106] (LE: 2a). 18FDG Positron-emission tomography (PET) is not recommended in primary staging. [117, 131] (LE: 1b).

Emerging technologies for differentiation of RCC subtypes has a growing body of evidence with regard to prostate-specific membrane antigen (PSMA) positron emission tomography (PET)-CT [132], ^{99}TC sestamibi SPECT/CT and ^{89}Zr-DFO-Girentuximab PET-CT [39, 40, 133]. Additionally some of these modalities are being evaluated for staging purposes [40]. Currently, the level of published evidence is not sufficient in terms of external validation to allow any guideline recommedation to be made.

*5.2.4 **Radiographic investigations to evaluate RCC metastases***

Chest CT is accurate for chest staging [90, 91, 134-136] (LE: 3). Use of nomograms to calculate risk of lung metastases have been proposed based on tumour size, clinical stage and presence of systemic symptoms [137, 138]. These are based on large, retrospective datasets, and suggest that chest CT may be omitted in patients with cT1a and cN0, and without systemic symptoms, anaemia or thrombocythemia, due to the low incidence of lung metastases (< 1%) in this group of patients. There is a consensus that most bone metastases are symptomatic at diagnosis; thus, routine bone imaging is not generally indicated [134, 139, 140] (LE: 3). However, bone scan, brain CT, or MRI may be used in the presence of specific clinical or laboratory signs and symptoms [139, 141, 142] (LE: 3). A prospective comparative blinded study involving 92 consecutive mRCC patients treated

with first-line vascular endothelial growth factor receptor (VEGFR)-tyrosine kinase inhibitor (TKI) (median follow-up 35 months) found that whole-body DWI/MRI detected a statistically significant higher number of bony metastases compared with conventional thoraco-abdomino-pelvic contrast-enhanced CT, with higher number of metastases being an independent prognostic factor for progression-free survival (PFS) and overall survival (OS) [143].

The incidence of brain metastasis without neurological symptoms was retrospectively evaluated in 1,689 mRCC patients, selected to be included in 68 clinical trials between 2001-2013 [144]. All patients had a mandatory brain screening by CT/MRI. Seventy-two patients (4.3%) were diagnosed with occult brain metastases, of whom 39% multi-focal. Most patients (61%) were International Metastatic Renal Cancer Database Consortium (IMDC) intermediate risk and 26% were favourable risk. A majority (86%) of the patients had > 2 extracranial metastatic sites, including lung metastases in 92%. After predominantly radiotherapy, performed in 93% of patients, a median OS of 10.3 months (range 7.0–17.9 months) was observed.

*5.2.5 **Bosniak classification of renal cystic masses***

This system classifies renal cysts into five categories, based on CT imaging appearance, to predict malignancy risk [145, 146] (LE: 3), and also advocates treatment for each category (Table 5.1). An updated Bosniak classification (2019) strengthened the classification and included MRI diagnostic criteria [75]; however, it requires further validation. According to a Meta-analysis based on 471 patients, the risk of maliganacy of Bosniak IIF-III, may be higher than with the old classification [147]. Until further validation, the imaging report should therefore identify which classification has been used. Lastly, the management of cystic renal tumours is also discussed in Section 3.5.8.

Table 5.1: Bosniak classification of renal cysts updated 2019 [75]

Bosniak classification / Imaging modality	**CT**	**MRI**
1 (Benign)	Well-defined, thin (≤ 2 mm) smooth wall; homogeneous simple fluid (-9 to 20 HU); no septa or calcifications; the wall may enhance	Well-defined, thin (≤ 2 mm) smooth wall; homogeneous simple fluid (signal intensity similar to CSF); no septa or calcifications; the wall may enhance
2 (Benign)	1. Cystic masses with thin (≤ 2 mm) and few (1–3) septa; septa and wall may enhance; may have calcification of any type 2. Homogeneous hyperattenuating (≥ 70 HU) masses at non-contrast CT 3. Homogeneous non-enhancing masses. 20 HU at renal mass protocol CT, may have calcification of any type† 4. Homogeneous masses -9 to 20 HU at non-contrast CT 5. Homogeneous masses 21 to 30 HU at portal venous phase CT 6. Homogeneous low-attenuation masses that are too small to characterise	1. Cystic masses with thin (≤ 2 mm) and few (1-3) enhancing septa; any non-enhancing septa; may have calcification of any type 2. Homogeneous masses markedly hyperintense at T2-weighted imaging (similar to CSF) at non-contrast MRI 3. Homogeneous masses markedly hyperintense at T1-weighted imaging (approximately 32.5 normal parenchymal signal intensity) at non-contrast MRI

2F (Follow-up, up to five years. Some are malignant.)	Cystic masses with a smooth minimally thickened (3 mm) enhancing wall, or smooth minimal thickening (3 mm) of one or more enhancing septa, or many (≥ 4 mm) smooth thin (≤ 2 mm) enhancing septa	1. Cystic masses with a smooth minimally thickened (3 mm) enhancing wall, or smooth minimal thickening (3 mm) of one or more enhancing septa, or many (≥ 4 mm) smooth thin (≤2 mm) enhancing septa 2. Cystic masses that are heterogeneously hyperintense at unenhanced fat-saturated T1-weighted imaging
3 (Surgery or AS – see Chapter 7. Over 50% are malignant.)	One or more enhancing thick (≥ 4 mm width) or enhancing irregular (displaying ≤ 3 mm obtusely margined convex protrusion[s]) walls or septa	One or more enhancing thick (≥ 4 mm width) or enhancing irregular (displaying ≤ 3 mm obtusely margined convex protrusion[s]) walls or septa
4 (Surgery. Most are malignant.)	One or more enhancing nodule(s) (≥4 mm convex protrusion with obtuse margins, or a convex protrusion of any size that has acute margins	One or more enhancing nodule(s) (≥4 mm convex protrusion with obtuse margins, or a convex protrusion of any size that has acute margins)

5.3 Renal tumour biopsy

*5.3.1 **Indications and rationale***

Percutaneous renal tumour biopsy can reveal histology of radiologically indeterminate renal masses and can be considered in patients who are candidates for AS of small masses, to obtain histology before ablative treatments, and to select the most suitable medical and surgical treatment strategy in the setting of metastatic disease [148-153] (LE: 3).

A multicentre study assessing 542 surgically removed SRMs showed that the likelihood of benign findings at pathology is significantly lower in centres where biopsies are performed (5% vs. 16%), suggesting that biopsies can reduce surgery for benign tumours and the potential for short-term and long-term morbidity associated with these procedures [154]. In a recent series of patients who underwent a percutaneous biopsy for a SRM, active treatment (surgery or cryotherapy) was avoided in 50/182 patients (27.5%) because of a benign diagnosis at biopsy [155].

Renal biopsy is not indicated in comorbid and frail patients who can be considered only for conservative management (watchful waiting) regardless of biopsy results. Due to the high diagnostic accuracy of abdominal imaging, renal tumour biopsy is not necessary in patients with a contrast-enhancing renal mass for whom surgery is planned (LE: 4).

Core biopsies of cystic renal masses have a lower diagnostic yield and accuracy and are not recommended, unless areas with a solid pattern are present (Bosniak IV cysts) [148, 151, 156] (LE: 2b/3). Histological characterisation by percutaneous biopsy of undefined retroperitoneal masses at imaging may be useful for decision making, especially in the younger patient population.

*5.3.2 **Technique***

Percutaneous sampling can be performed under local anaesthesia with needle core biopsy and/or fine needle aspiration (FNA). Biopsies can be performed under US or CT guidance, with a similar diagnostic yield [151, 157] (LE: 2b). Eighteen-gauge needles are ideal for core biopsies, as they result in low morbidity and provide sufficient tissue for diagnosis [148, 152, 158] (LE: 2b). A coaxial technique allowing multiple biopsies through a coaxial cannula should always be used to avoid potential tumour seeding [148, 152] (LE: 3).

Core biopsies are preferred for the characterisation of solid renal masses while a combination with FNA can provide complimentary results and improve accuracy for complex cystic lesions [156, 159, 160] (LE: 2a). A SR and meta-analysis of the diagnostic performance and complications of renal tumour biopsy was performed by the Panel, including 57 publications and a total of 5,228 patients. Needle core biopsies were found to have better accuracy for the diagnosis of malignancy compared with FNA [156]. Other studies showed that solid pattern, larger tumour size and exophytic location are predictors of a diagnostic core biopsy [148, 151, 157] (LE: 2b).

*5.3.3 **Diagnostic yield and accuracy***

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 [156] (LE: 2b). However, 0–22.6% of core biopsies are non-diagnostic (8% in the meta-analysis) [149-153, 157, 158, 161] (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%) [148, 162-164].

Accuracy of renal tumour biopsies for the diagnosis of tumour histotype is good. The median concordance rate between tumour histotype on renal tumour biopsy and on the surgical specimen of the following PN or RN was 90.3% in the pooled analysis [156].

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 vs. low grade) [156] (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 [148, 151, 165, 166] (LE: 2b). Peripheral biopsies are preferable for larger tumours, to avoid areas of central necrosis [167] (LE: 2b). In cT2 or greater renal masses, multiple core biopsies taken from at least four separate solid enhancing areas in the tumour were shown to achieve a higher diagnostic yield and a higher accuracy to identify sarcomatoid features, without increasing the complication rate [168].

*5.3.4 **Morbidity***

Overall, percutaneous biopsies have a low morbidity [156]. Tumour seeding along the needle tract has been regarded as anecdotal in large series and pooled analyses on renal tumour biopsies. Especially the coaxial technique has been regarded as a safe method to avoid any seeding of tumour cells. However, authors recently reported on seven patients in whom tumour seeding was identified on histological examination of the resection specimen after surgical resection of RCC following diagnostic percutaneous biopsy [169]. Six of the seven cases were of the pRCC type. The clinical significance of these findings is still uncertain but only one of these patients developed local tumour recurrence at the site of the previous biopsy [169].

Spontaneously resolving subcapsular/perinephric haematomas are reported in 4.3% of cases in a pooled analysis, but clinically significant bleeding is unusual (0-1.4%; 0.7% in the pooled analysis) and generally self-limiting [156].

Percutaneous biopsy of renal hilar masses is technically feasible with a diagnostic yield similar to that of cortical masses, but with significantly higher post-procedural bleeding compared with cortical masses [170].

*5.3.5 **Genetic assessment***

Renal cancer can be related to an inherited or *de novo* monogenic germline alteration and this recognition has significant implications [171]. Hereditary kidney cancer is thought to account for 5-8% of all kidney cancer cases, although this number is likely an underestimation since a more recent study found germline mutations in up to 38% of all metastatic kidney cancer patients [172] (see Section 3.4.4. - Hereditary kidney tumours). Patients with a germline predisposition to kidney cancer often require multidisciplinary approaches, it is critical for clinicians to be familiar with how and when referral for counselling is warranted, methods of genetic testing, implications of the findings, screening of at-risk (non-renal) organs, and the screening protocol for family members. Well-defined renal cancer management strategies exist, and specific therapeutic strategies are available or in development (see Section 3.4.4). Lack of a syndromic manifestation does not exclude a genetic contribution to cancer development. Moreover, other genetic components or polymorphisms are heritable and may confer a mildly increased risk. When several risk alleles are present, they can significantly increase cancer risk.

Many factors are associated with an increased risk of hereditary renal cancer syndromes. For instance, even in the absence of clinical manifestations and personal/family history, an age of onset of 46 years or younger should trigger consideration for genetic counselling/germline mutation testing [46]. Moreover, presence of bilateral or multifocal tumours/cysts and/or a first- or second-degree relative with RCC and/or a close blood relative with a known pathogenic variant significantly increases the risk to detect hereditary cancer. The presence of renal cysts can be associated with BHD and VHL, and form part of the clinical diagnostic spectrum. Moreover, specific histologic characteristics can support differential diagnosis of a particular RCC syndrome (e.g., multifocal papillary histology, hereditary fumarate hydratase-deficient RCC, RCC with fumarate hydratase deficiency, multiple chromophobe, oncocytoma or oncocytic hybrid, succinate dehydrogenase-deficient RCC histology). Finally, additional tuberous sclerosis complex criteria should be assessed in individuals with AML [46, 173-181].

If additional risk factors are established in a patient, referral to a comprehensive clinical care centre, or a hospital with demonstrated expertise in managing hereditary cancer syndromes, will provide a dedicated working team, tailored clinical decisions, research translational programme, appropriate patient psychosocial support, and prospective collection of clinical data and biological samples. This can contribute to a better patient's care and further improvements in cancer care.

5.4 Summary of evidence and recommendations for the diagnostic assessment of RCC

Summary of evidence	LE
Contrast enhanced multi-phasic CT has a high sensitivity and specificity for characterisation and detection of RCC, invasion, tumour thrombus and mRCC.	2a
Magnetic resonance imaging has a slightly higher sensitivity and specificity for small cystic renal masses and tumour thrombi as compared to CT.	2a
Contrast enhanced US has a high sensitivity and specificity for characterisation of renal masses.	2a
Renal mass biopsies are associated with reduced overtreatment of benign masses and offers patients additional information (i.e. grade, subtype) for an informed decision regarding optimal management.	3
Ultrasound, power-Doppler US and positron-emission tomography CT have a low sensitivity and specificity for detection and characterisation of RCC.	2a

Recommendations	Strength rating
Use multi-phasic contrast-enhanced computed tomography (CT) of abdomen and chest for the diagnosis and staging of renal tumours.	Strong
Omit chest CT in patients with incidentally noted cT1a disease due to the low risk of lung metastases in this cohort.	Weak
Use magnetic resonance imaging (MRI) to better evaluate venous involvement, reduce radiation or avoid intravenous CT contrast medium.	Weak
Use non-ionising modalities, including MRI and contrast-enhanced ultrasound, for further characterisation of small renal masses, tumour thrombus and differentiation of unclear renal masses, in case the results of contrast-enhanced CT are indeterminate.	Strong
Offer brain CT/MRI in metastatic patients when systemic therapy or cytoreductive nephrectomy is considered.	Weak
Do not routinely use bone scan and/or positron-emission tomography CT for staging of renal cell carcinoma.	Weak
Perform a renal tumour biopsy before ablative therapy and systemic therapy without previous pathology.	Strong
Perform a percutaneous biopsy in select patients who are considering active surveillance.	Weak
Use a coaxial technique when performing a renal tumour biopsy.	Strong
Do not perform a renal tumour biopsy of cystic renal masses unless a significant solid component is visible at imaging.	Strong
Use a core biopsy technique rather than fine needle aspiration for histological characterisation of solid renal tumours.	Strong

5.5 Summary of evidence and recommendations for genetic assessment of RCC

Summary of evidence	LE
Hereditary kidney cancer is thought to account for 5-8% of all kidney cancer cases, though that number is likely an underestimate.	3
In case of renal cancer, if patient's age is 46 years or younger, and/or with bilateral or multifocal tumours and/or with a first or second-degree relative with RCC and/or with a close blood relative with a known pathogenic variant and/or with specific histologic characteristics (see text), the risk of hereditary cancer is significantly higher.	3
Hereditary RCC detection has unique implications for decision-making and follow-up.	3

Recommendations	Strength rating
Perform a genetic evaluation in patients aged ≤ 46 years, with bilateral or multifocal tumours and/or a first- or second-degree relative with RCC and/or a close blood relative with a known pathogenic variant and/or specific histologic characteristics which suggest the presence of a hereditary form of RCC.	Strong
Refer patients to a cancer geneticist or to a Comprehensive Clinical Care Centre in case of suspected hereditary RCC.	Strong

6. PROGNOSTIC FACTORS

6.1 Classification

Prognostic factors can be classified into: anatomical, histological, clinical, and molecular.

6.2 Anatomical factors

Tumour size, venous invasion and extension, collecting system invasion, perinephric- and sinus fat invasion, adrenal involvement, and LN and distant metastasis are included in the TNM classification system [182, 183] (Table 4.1).

6.3 Histological factors

Histological factors include tumour grade, RCC subtype, lymphovascular invasion, tumour necrosis, and invasion of the collecting system [184, 185]. Tumour grade is considered one of the most important histological prognostic factors. Fuhrman nuclear grade [186] has now been replaced by the WHO/ISUP grading classification [187]. This relies solely on nucleolar prominence for grade 1-3 tumours, allowing for less inter-observer variation [188]. It has been shown that the WHO/ISUP grading provides superior prognostic information compared to Fuhrman grading, especially for grade 2 and grade 3 tumours [189]. Rhabdoid and sarcomatoid changes can be found in all RCC types and are equivalent to grade 4 tumours. Sarcomatoid changes are more often found in chRCC than other subtypes [190]. The percentage of the sarcomatoid component appears to be prognostic as well, with a larger percentage of involvement being associated with worse survival. There is no agreement on the optimal prognostic cut-off for sub-classifying sarcomatoid changes [191, 192], although 20% has been suggested to distinguish focal and extensive amount of sarcomatoid features [193]. The WHO/ISUP grading system is applicable to both ccRCC and pRCC. It is currently not recommended to grade chRCC. However, a recent study suggested a two-tiered chRCC grading system (low vs. high grade) based on the presence of sarcomatoid differentiation and/or tumour necrosis, which was statistically significant on multivariable analysis [194]. Both the WHO/ISUP and chRCC grading systems need to be validated for prognostic systems and nomograms [187].

Renal cell carcinoma subtype is regarded as another important prognostic factor. On univariable analysis, patients with chRCC vs. pRCC vs. ccRCC had a better prognosis [195, 196] (Table 6.1). However, prognostic information provided by the RCC type is lost when stratified according to tumour stage [196, 197] (LE: 3).

In a recent cohort study of 1,943 patients with ccRCC and pRCC significant survival differences were only shown between pRCC type I and ccRCC [198]. Papillary RCC has been traditionally divided into type 1 and 2, but a subset of tumours shows mixed features. For more details, see Section 3.2 – Histological diagnosis. Data also suggest that type 2 pRCC is a heterogeneous entity with multiple molecular subgroups [199]. Some studies suggest poorer survival for type 2 than type 1 [200], but this association is often lost in the multivariable analysis [201]. A meta-analysis did not show a significant survival difference between both types [202, 203].

TFE3 re-arranged RCC (formerly called RCC with Xp11.2 translocation) has a poor prognosis [204]. Its incidence is low, but its presence should be systematically assessed in young patients. Renal cell carcinoma type classification has been confirmed by cytogenetic and genetic analyses [205-207] (LE: 2b). Surgically excised malignant complex cystic masses contain ccRCC in the majority of cases, and more than 80% are pT1. In a recent series, 5-year CSS was 98% [208]. Differences in tumour stage, grade and CSS between RCC types are illustrated in Table 6.1.

Table 6.1: Baseline characteristics and cancer-specific survival of surgically treated patients by RCC type [145]

Survival time	% RCC	% Sarcomatoid	% T3-4	% N1	% M1	% 10 year CSS (%)
Clear-cell RCC	80	5	33	5	15	62
Papillary RCC	15	1	11	5	3	86
Chromophobe RCC	5	8	15	4	4	86

CSS = cancer-specific survival.

In all RCC types, prognosis worsens with stage and histopathological grade (Table 6.2). The 5-year OS for all types of RCC is 49%, which has improved since 2006, probably due to an increase in incidentally detected RCCs and new systemic treatments [209, 210]. Although not considered in the current N classification, the number of metastatic regional LNs is an important predictor of survival in patients without distant metastases [211].

Table 6.2: Cancer-specific survival by stage [212]

Grade	HR (95% CI)
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)

CI = confidence interval; HR = hazard ratio.

6.4 Clinical factors

Clinical factors include performance status (PS), local symptoms, cachexia, anaemia, platelet count, neutrophil count, lymphocyte count, C-reactive protein (CRP) [213], albumin, and various indices deriving from these factors such as the neutrophil-to-lymphocyte ratio (NLR) [103, 214-219] (LE: 3). As a marker of systemic inflammatory response, a high pre-operative NLR has been associated with poor prognosis [220], but there is significant heterogeneity in the data and no agreement on the optimal prognostic cut-off. Even though obesity is an aetiological factor for RCC, it has also been observed to provide prognostic information. A high body mass index (BMI) appears to be associated with improved survival outcomes in both non-metastatic and metastatic RCC [221-223]. This association is linear with regards to cancer-specific mortality (CSM), while obese RCC patients show increasing all-cause mortality with increasing BMI [224]. There is also evolving evidence on the prognostic value of body composition indices measured on cross-sectional imaging, such as sarcopenia and fat accumulation [219, 225, 226].

6.5 Molecular factors

Numerous molecular markers such as carbonic anhydrase IX (CaIX), VEGF, HIF, Ki67 (proliferation), p53, p21 [227], PTEN (phosphatase and tensin homolog) cell cycle [228], E-cadherin, osteopontin [229] CD44 (cell adhesion) [230, 231], CXCR4 [232], PD-L1 [233], miRNA, SNPs, gene mutations, and gene methylations have been investigated (LE: 3) [234]. While the majority of these markers are associated with prognosis and many improve the discrimination of current prognostic models, there has been very little emphasis on external validation studies. Furthermore, there is no conclusive evidence on the value of molecular markers for treatment selection in mRCC [213, 233, 235]. Their routine use in clinical practice is therefore not recommended.

Several prognostic and predictive marker signatures have been described for specific systemic treatments in mRCC. In the JAVELIN Renal 101 trial (NCT02684006), a 26-gene immunomodulatory gene signature predicted PFS in those treated with avelumab plus axitinib, while an angiogenesis gene signature was associated with PFS for sunitinib. Mutational profiles and histocompatibility leukocyte antigen (HLA) types were also associated with PFS, while programmed death-ligand 1 (PD-L1) expression and tumour mutational burden were not [236]. In IMmotion151 (NCT02420821), a T effector/IFN-γ-high or angiogenesis-low gene expression signature predicted improved PFS for atezolizumab plus bevacizumab compared to sunitinib. The angiogenesis-high gene expression signature correlated with longer PFS in patients treated with sunitinib [237]. In CheckMate 214 (NCT02231749), a higher angiogenesis gene signature score was associated with better overall response rates

and PFS for sunitinib, while a lower angiogenesis score was associated with higher ORR in those treated with nivolumab plus ipilimumab. Progression-free survival > 18 months was more often seen in patients with higher expression of Hallmark inflammatory response and Hallmark epithelial mesenchymal transition gene sets [219].

Urinary and plasma Kidney-Injury Molecule-1 (KIM-1) has been identified as a potential diagnostic and prognostic marker. KIM-1 concentrations were found to predict RCC up to five years prior to diagnosis and were associated with a shorter survival time [238]. KIM-1 is a glycoprotein marker of acute proximal tubular injury and therefore mainly expressed in RCC derived from the proximal tubules such as ccRCC and pRCC [239]. While early studies are promising, more high-quality research is required. Several retrospective studies and large molecular screening programmes have identified mutated genes and chromosomal changes in ccRCC with distinct clinical outcomes. The expression of the BAP1 and PBRM1 genes, situated on chromosome 3p in a region that is deleted in more than 90% of ccRCCs, have shown to be independent prognostic factors for tumour recurrence [240-242]. These published reports suggest that patients with BAP1- mutant tumours have worse outcomes compared with patients with PBRM1-mutant tumours [241]. Loss of chromosome 9p and 14q have been consistently shown to be associated with poorer survival [243-245]. The TRACERx renal consortium has proposed a genetic classification based on RCC evolution (punctuated vs. branched vs. linear), which correlates with tumour aggressiveness and survival [244]. Additionally, a 16-gene signature was shown to predict disease-free survival (DFS) in patients with non-metastatic RCC [246]. However, these signatures have not been validated by independent researchers yet.

6.6 Prognostic models

Prognostic models combining independent prognostic factors have been developed and externally validated [247-254]. These models are more accurate than TNM stage or grade alone for predicting clinically relevant oncological outcomes (LE: 3). Before being adopted, new prognostic models should be evaluated and compared to current prognostic models with regards to discrimination, calibration and net benefit. Pathological prognostic factors are used in the Leibovich 2003 score/groups for clear cell [250]. There are prognostic models for non-clear cell RCC, like the VENUSS score for papillary RCC [201]. Although both were validated in several studies and showed superior discrimination to other prognostic models, molecular markers are needed [255-258]. In metastatic disease, risk groups assigned by the Memorial Sloan Kettering Cancer Centre (MSKCC) (primarily created in the pre-targeted therapy era and validated in patients receiving targeted therapy) and the IMDC (initially created in the targeted therapy era) differ in 23% of cases [259]. The IMDC model has been used in most of the recent RCTs, including those with immune checkpoint inhibitors (ICIs), and may therefore be the preferred model for clinical practice. The discrimination of the IMDC models improves by additional variables, such as presence of brain metastasis, bone metastasis, liver metastasis, NLR and platelet count [260-263]. Tables 6.3 and 6.4 summarise the current most relevant prognostic models.

6.7 Summary of evidence and recommendations for prognostic factors

Summary of evidence	LE
In RCC patients, TNM stage, tumour size, grade, and RCC subtype provide important prognostic information.	2a
The 2003 Leibovich score is a validated prognostic model to predict the short- and long-term risk of metastasis in individual patients with sporadic, unilateral pT1-4 N0/+ M0 clear cell renal cell carcinoma.	2b
The VENUSS score is a validated prognostic model to predict the short- and long-term risk of disease recurrence in individual patients with sporadic, unilateral pT1-4 N0/+ M0 papillary renal cell carcinoma.	2b

Recommendations	Strength rating
Use the current Tumour, Node, Metastasis classification system.	Strong
Use the WHO/ISUP grading system and classify renal cell carcinoma type.	Strong
Use prognostic models in localised and metastatic disease.	Strong
Use the 2003 Leibovich scoring model for risk stratification of localised and locally advanced clear cell renal cell carcinoma.	Weak
Use the VENUSS scoring model for risk stratification of localised and locally advanced papillary renal cell carcinoma.	Weak
Do not routinely use molecular markers to assess prognosis.	Strong

Table 6.3: Prognostic models for localised RCC

Prognostic model	Subtype*	Risk factors/prognostic factors
UISS** [264]	All	1. ECOG PS 2. T classification 3. N classification (N+ classified as metastatic) 4. Grade T1N0M0G1-2, ECOG PS 0: low-risk disease T3N0M0G2-4, ECOG PS ≥ 1 OR T4N0M0: high-risk disease Any other N0M0: intermediate-risk disease
Leibovich score/ model 2003 [250]	CC	1. T classification (pT1a: 0, pT1b: 1, pT2:3, pT3-4: 4 points) 2. N classification (pNx/N0: 0, pN+: 2 points) 3. Tumour size (< 10 cm: 0, ≥ 10 cm: 1 point) 4. Grade (G1-2: 0, G3: 1, G4: 3 points) 5. Tumour necrosis (absent: 0, present: 1 point) 0-2 points: low-risk disease 3-5 points: intermediate-risk disease 6 or more points: high-risk disease
Leibovich score/ model 2018 [265]	CC, P, CH	ccRCC • Progression (9 factors): constitutional symptoms, grade, tumour necrosis, sarcomatoid features, tumour size, perinephric or sinus fat invasion, tumour thrombus level, extension beyond kidney, nodal involvement. • Cancer-specific survival (12 factors): age, ECOG PS, constitutional symptoms, adrenalectomy, surgical margins, grade, tumour necrosis, sarcomatoid features, tumour size, perinephric or sinus fat invasion, tumour thrombus, nodal involvement. • No risk groups /prognostic groups. pRCC • Low risk (group 1): grade 1-2, no fat invasion, no tumour thrombus. • Intermediate risk (group 2): grade 3, no fat invasion, no tumour thrombus. • High risk (group 3): grade 4 or fat invasion or any level tumour thrombus. chRCC • Low risk (group 1): no fat invasion, no sarcomatoid differentiation, no nodal involvement. • Intermediate risk (group 2): fat invasion and no sarcomatoid differentiation and no nodal involvement. • High risk (group 3): sarcomatoid differentiation or nodal involvement.
VENUSS score/ model*** [201, 255]	P	1. T classification (pT1: 0, pT2: 1, pT3-4: 2 points) 2. N classification (pNx/pN0: 0, pN1: 3 points) 3. Tumour size (≤ 4 cm: 0, > 4 cm: 2 points) 4. Grade (G1/2: 0, G3/4: 2 points) 5. Tumour thrombus (absent: 0, present: 2 points) 0-2 points: low-risk disease 3-5 points: intermediate-risk disease 6 or more points: high-risk disease

GRANT score/ model**** [266]	All	1. Age > 60 years 2. T classification = T3b, pT3c or pT4 3. N classification = pN1 4. (Fuhrman) grade = G3 or G4 0-1 factors: favourable-risk disease 2 or more factors: unfavourable-risk disease

* *ccRCC = clear-cell RCC; ECOG = Eastern Cooperative Oncology Group; pRCC = papillary RCC; chRCC = chromophobe RCC; PS = performance status.*

** *University of California Integrated Staging system. Available at https://www.mdcalc.com/ucla-integratedstaging-system-uiss-renal-cell-carcinoma-rcc.*

*** *Venous extension, Nuclear grade, Size, Stage. Available at https://www.evidencio.com/models/show/2369.*

**** *Grade, Age, Nodes and Tumour.*

Table 6.4: Prognostic models for metastatic RCC

Prognostic model	Subtype	Risk factors/prognostic factors
MSKCC [267]**	All	1. Karnofsky PS [268]* < 80% 2. Interval from diagnosis to systemic treatment < 1 year 3. Haemoglobin < Lower Limit of Normal 4. Corrected calcium >10mg/dL/> 2.5 mmol/L 5. LDH > 1.5x Upper Limit of Normal 0 factors: favourable-risk disease 1-2 factors: intermediate-risk disease 3-5 factors: poor-risk disease
IMDC [269]***	All	1. Karnofsky PS [268]* < 80% 2. Interval from diagnosis to treatment < 1 year 3. Haemoglobin < lower limit of normal 4. Corrected calcium > upper limit of normal (i.e. > 10.2 mg/dL) 5. Neutrophil count > upper limit of normal (i.e. > 7.0×10⁹/L) 6. Platelet count > upper limit of normal (i.e. > 400,000) 0 factors: favourable-risk disease 1-2 factors: intermediate-risk disease 3-6 factors: poor-risk disease

IMDC = International Metastatic Renal Cancer Database Consortium; LDH = lactate dehydrogenase; MSKCC = Memorial Sloan Kettering Cancer Center; PS = performance status.

* *Karnofsky performance status calculator: https://www.thecalculator.co/health/Karnofsky-Score-for-Performance-Status-Calculator-961.html.*

** *MSKCC: https://www.mdcalc.com/memorial-sloan-kettering-cancer-center-mskcc-motzer-score-etastaticrenal-cell-carcinoma-rcc.*

*** *IMDC: https://www.mdcalc.com/imdc-international-metastatic-rcc-database-consortium-risk-score-rcc.*

7. DISEASE MANAGEMENT

7.1 Treatment of localised RCC

7.1.1 ***Introduction***

Sections 7.1.2 and 7.2.4.2 are underpinned by a SR which includes all relevant published literature comparing surgical management of localised RCC (T1–2N0M0). Randomised or quasi-RCTs were included. However, due to the very limited number of RCTs, non-randomised studies (NRS), prospective observational studies with controls, retrospective matched-pair studies, and comparative studies from the databases of well-defined registries were also included. Historically, surgery has been the benchmark for the treatment of localised RCC.

*7.1.2 **Surgical treatment***

7.1.2.1 Nephron-sparing surgery versus radical nephrectomy in localised RCC

7.1.2.1.1 T1 RCC

Outcome 1: Cancer-specific survival

Most studies comparing the oncological outcomes of PN and RN are retrospective and include cohorts of varied and, overall, limited size [270, 271]. There is only one, prematurely closed, prospective RCT including patients with organ-confined RCCs of limited size (< 5 cm) published, showing comparable non-inferiority of CSS for PN vs. RN (HR: 2.06 [95% CI: 0.62–6.84]) [272].

Outcomes 2 & 3: Overall mortality and renal function

Partial nephrectomy preserved kidney function better after surgery, thereby potentially lowering the risk of development of cardiovascular disorders [270, 273-277]. When compared with a radical surgical approach, several retrospective analyses of large databases have suggested a decreased cardiovascular-specific mortality [274, 278] as well as improved OS for PN compared to RN. However, in some series this held true only for younger patients and/or patients without significant comorbidity at the time of the surgical intervention [279, 280]. An analysis of the U.S. Medicare database [281] could not demonstrate an OS benefit for patients ≥ 75 years of age when RN or PN were compared with non-surgical management.

Conversely, another series that addressed this question and included Medicare patients, suggested an OS benefit in older patients (75-80 years) when subjected to surgery rather than non-surgical management. Shuch *et al.*, compared patients who underwent PN for RCC with a non-cancer healthy control group via a retrospective database analysis; showing an OS benefit for the cancer cohort [282]. These conflicting results may be an indication that unknown statistical confounders hamper the retrospective analysis of population-based tumour registries. In the only prospectively randomised, but prematurely closed, heavily underpowered, trial, PN seems to be less effective than RN in terms of OS in the intention to treat (ITT) population (HR: 1.50 [95% CI: 1.03–2.16]). However, in the targeted RCC population of the only RCT, the trend in favour of RN was no longer significant [272]. Taken together, the OS advantage suggested for PN vs. RN remains an unresolved issue.

Patients with a normal pre-operative renal function and a decreased GFR due to surgical treatment (either RN or PN), generally present with stable long-term renal function [277]. Adverse OS in patients with a pre-existing GFR reduction does not seem to result from further renal function impairment following surgery, but rather from other medical comorbidities causing pre-surgical chronic kidney disease (CKD) [283]. However, in particular in patients with pre-existing CKD, PN is the treatment of choice to limit the risk of development of ESRD which requires haemodialysis. Huang *et al.*, found that 26% of patients with newly diagnosed RCC had an GFR ≤ 60 mL/min, even though their baseline serum creatinine levels were in the normal range [106].

Outcomes 4 & 5: Peri-operative outcomes and quality of life

In terms of the intra- and peri-operative morbidity/complications associated with PN vs. RN, the European Organisation for Research and Treatment of Cancer (EORTC) randomised trial showed that PN for small, easily resectable, incidentally discovered RCC, in the presence of a normal contralateral kidney, can be performed safely with slightly higher complication rates than after RN [284].

Only a limited number of studies are available addressing quality of life (QoL) following PN vs. RN, irrespective of the surgical approach used (open vs. minimally invasive). Quality of life was ranked higher following PN as compared to RN, but in general patients' health status deteriorated following both approaches [284, 285].

In view of the above, and since oncological safety (CSS and RFS) of PN, so far, has been found non-differing from RN outcomes, PN is the treatment of choice for T1 RCC since it preserves kidney function better and in the long term PN potentially limits the incidence of cardiovascular disorders and

development of ESRD and the need for haemodialysis. Irrespective of the available data, in frail patients, treatment decisions should be individualised, weighing the risks and benefits of PN vs. RN, the increased risk of peri-operative complications, and the risk of developing or worsening of CKD post-operatively.

7.1.2.1.2 T2 RCC

There is very limited evidence on the optimal surgical treatment for patients with larger renal masses (T2). Some retrospective comparative studies of PN vs. RN for T2 RCC have been published [286]. A trend for lower tumour recurrence- and CSM is reported in PN groups. The estimated blood loss is reported to be higher for PN groups, as is the likelihood of post-operative complications [286]. A multicentre study compared the survival outcomes in patients with larger (> 7 cm) ccRCC treated with PN vs. RN with long-term follow- up (median 102 months). Compared to the RN group, the PN group had a significantly longer median OS (p = 0.014) and median CSS (p = 0.04) [287]. Retrospective comparative studies of cT1 and cT2 RCC patients upstaged to pT3a RCC show contradictory results: some reports suggest similar oncologic outcomes between PN and RN [288], whilst another recent report suggests that PN of clinical T1 in pathologically upstaged pT3a of cT1 RCC is associated

with a significantly shorter RFS than RN [289]. Overall, the level of the evidence is low. These studies including T2 masses all have a high risk of selection bias due to imbalance between the PN and RN groups regarding patient's age, comorbidities, tumour size, stage, and tumour position. These imbalances in covariation factors may have a greater impact on patient outcome than the choice of PN or RN. The Panel's confidence in the results is limited and the true effects may be substantially different.

In view of the above, the risks and benefits of PN should be discussed with patients with T2 tumours. In this setting PN should be considered, if technically feasible, in patients with a solitary kidney, bilateral renal tumours or CKD with sufficient parenchymal volume preserved to allow sufficient post-operative renal function.

7.1.2.1.3 T3 RCC

A meta-analysis of nine articles including 1,278 patients with PN and 2,113 patients with RN for pT3a RCC showed no difference in CSS, OS, CSM and RFS, indicating that PN techniques can be used for functional benefits and if technically feasible [290].

7.1.2.2 Associated procedures

7.1.2.2.1 Adrenalectomy

One prospective NRS compared the outcomes of RN with, or without, ipsilateral adrenalectomy [291]. Multivariable analysis showed that upper pole location was not predictive of adrenal involvement, but tumour size was. No difference in OS at five or ten years was seen with, or without, adrenalectomy. Adrenalectomy was justified using criteria based on radiographic- and intra-operative findings. Only 48 of 2,065 patients underwent concurrent ipsilateral adrenalectomy of which 42 of the 48 interventions were for benign lesions [291].

7.1.2.2.2 Lymph node dissection for clinically negative lymph nodes (cN0)

The indication for LN dissection (LND) together with PN or RN is still controversial [292]. The clinical assessment of LN status is based on the detection of an enlargement of LNs either by CT/MRI or intra-operative palpability of enlarged nodes. Less than 20% of suspected metastatic nodes (cN+) are positive for metastatic disease at histopathological examination (pN+) [293]. Both CT and MRI are unsuitable for detecting malignant disease in nodes of normal shape and size [294]. For clinically positive LNs (cN+) see Section 7.2.2.

Smaller retrospective studies have suggested a clinical benefit associated with a more or less extensive LND, preferably in patients at high risk for lymphogenic spread. In a large retrospective study, the outcomes of RN with, or without, LND, in patients with high-risk non-mRCC were compared using a propensity score analysis. In this study LND was not significantly associated with a reduced risk of distant metastases, cancer- specific or all-cause mortality. The extent of the LND was not associated with improved oncologic outcomes [295]. The number of LN metastases (< / > 4) as well as the intra- and extra-capsular extension of intra-nodal metastasis correlated with the patients´ clinical prognosis in some studies [294, 296-298]. Better survival outcomes were seen in patients with a low number of positive LNs (< 4) and no extra-nodal extension. Based on a retrospective Surveillance, Epidemiology and End Results (SEER) database analysis of > 9,000 patients no effects of an extended LND (eLND) on the disease-specific survival (DSS) of patients with pathologically- confined negative nodes was demonstrated [299]. However, in patients with pathologically proven lymphogenic spread (pN+), an increase of 10 for the number of nodes dissected resulted in a 10% absolute increase in DSS.

In addition, in a larger cohort of 1,983 patients, Capitanio *et al.*, demonstrated that eLND results in a significant prolongation of CSS in patients with unfavourable prognostic features (e.g., sarcomatoid differentiation, large tumour size) [300]. As to morbidity related to eLND, a retrospective propensity score analysis from a large single-centre database showed that eLND is not associated with an increased risk of Clavien grade > 3 complications. Furthermore, LND was not associated with length of hospital stay or estimated blood loss [301].

Only one prospective RCT evaluating the clinical value of LND combined with surgical treatment of primary RCC has been published so far. With an incidence of LN involvement of only 4%, the risk of lymphatic spread appears to be very low. Recognising the latter, only a staging effect was attributed to LND [293]. This trial included a very high percentage of patients with pT2 tumours, which are not at increased risk for LN metastases. Only 25% of patients with pT3 tumours underwent a complete LND and the LN template used by the authors was not clearly stated.

The optimal extent of LND remains controversial. Retrospective studies suggest that an eLND should involve the LNs surrounding the ipsilateral great vessel and the inter-aortocaval region from the crus of the diaphragm to the common iliac artery. Involvement of inter-aortocaval LNs without regional hilar involvement is reported in up to 35-45% of cases [294, 302, 303]. At least fifteen LNs should be removed [300, 304]. Sentinel LND is an investigational technique [305, 306].

7.1.2.2.3 Embolisation

Before routine nephrectomy, tumour embolisation has no benefit [307, 308]. In patients unfit for surgery, or with non-resectable disease, embolisation can control symptoms, including visible haematuria or flank pain [309]. These indications will be revisited 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 for the treatment of localised RCC

Summary of evidence	LE
The oncological outcome in terms of OS following PN equals that of RN in patients with c/p T1 RCC.	1b
Retrospective studies suggest that oncological outcomes are similar following PN vs. RN in patients with larger (≥ 7 cm) RCC. Post-operative complication rates are higher in PN patients.	3b
Ipsilateral adrenalectomy during RN or PN has no survival advantage in the absence of clinically evident adrenal involvement.	3
In patients with localised disease without radiographic evidence of LN metastases, a survival advantage of LND in conjunction with RN is not demonstrated in RCTs.	2b
Retrospective studies suggest a clinical benefit associated with LND in high-risk patients.	2b
In patients unfit for surgery with massive haematuria or flank pain, embolisation can be a beneficial palliative approach.	3

Recommendations	Strength rating
Offer surgery to achieve cure in localised renal cell cancer.	Strong
Offer partial nephrectomy (PN) to patients with T1 tumours.	Strong
Offer PN to patients with T2 tumours and a solitary kidney or chronic kidney disease, if technically feasible.	Weak
Do not perform ipsilateral adrenalectomy if there is no clinical evidence of invasion of the adrenal gland.	Strong
Do not offer an extended lymph node dissection to patients with organ-confined disease.	Weak
Offer embolisation to patients unfit for surgery presenting with massive haematuria or flank pain.	Weak

*7.1.3 **Radical and partial nephrectomy techniques***

7.1.3.1 Radical nephrectomy techniques

7.1.3.1.1 Open versus laparoscopic or robotic approach

No RCTs have assessed the oncological outcomes of laparoscopic vs. open RN. A retrospective comparative study with data retrieved from a national database studying the OS of open vs. minimally-invasive RN (laparoscopic RN or RARN) showed an OS benefit in the minimally invasive RN group, as well as in hospital stay, re-admission rate, and 30-day and 90-day mortality rate [310]. However, a SR did not demonstrate any survival difference in LRN and ORN [311].

Data from one SR [311] and two NRS [312, 313] showed a significantly shorter hospital stay and lower analgesic requirement for the laparoscopic RN group as compared with the open group. Convalescence time was also significantly shorter [313]. Surgical complication rates were low with very wide confidence intervals. There was no difference in complications, but operation time was significantly shorter in the open nephrectomy arm. Quality of life and perioperative outcomes were inconsistently defined, measured, or reported [270, 311] (LE: 2b, based on 1 low quality SR).

7.1.3.1.2 Laparoscopic versus robotic approach

Data of a large retrospective cohort study on robot-assisted laparoscopic vs. laparoscopic RN showed robot-assisted laparoscopic RN was not associated with increased risk of any or major complications but had a longer operating time and higher hospital costs compared with laparoscopic RN [314]. A SR and meta-analysis of seven studies including 1,832 patients showed no difference between the two approaches in peri-operative outcomes, including operative time, blood loss, conversion rates and complications [315]. A SR reported on robot-assisted laparoscopic vs. conventional laparoscopic RN, showing no substantial differences in local recurrence rates, nor in all-cause CSM [316].

7.1.3.1.3 Laparoscopic single port versus laparoscopic multiport approach

Similar results were seen in observational cohort studies comparing 'portless' and 3-port laparoscopic RN, with similar peri-operative outcomes [317, 318].

7.1.3.2 Partial nephrectomy techniques

7.1.3.2.1 Open versus laparoscopic approach

Studies comparing laparoscopic and open PN found no difference in PFS [319-322] and OS [321, 322] in centres with laparoscopic expertise. However, the oncological safety of laparoscopic vs. open PN has, so far, only been addressed in studies with relatively limited follow-up [323]. However, the higher number of patients treated with open surgery in this series might reflect a selection bias by offering laparoscopic surgery in case of a less complex anatomy [323]. The mean estimated blood loss was found to be lower with the laparoscopic approach [319, 321, 324], while post-operative mortality, deep vein thrombosis, and pulmonary embolism events were similar [319, 321]. Operative time is generally longer with the laparoscopic approach [320, 322] and warm ischaemia time is shorter with the open approach [319, 321, 324, 325]. The results for GFR decline are debatable, an RCT reported greater 3-12 months kidney function reduction in the open group [326] whilst in a matched-pair comparison, GFR decline was greater in the laparoscopic PN group in the immediate post-operative period [322], but not after 3.6 years follow-up. In another comparative study, the surgical approach was not an independent predictor for post-operative CKD [325]. Retroperitoneal and transperitoneal laparoscopic PN have similar peri-operative outcomes [327]. Simple tumour enucleation also had similar PFS and CSS rates compared to standard PN and RN in a large study [328]. The feasibility of laparo-endoscopic single-site PN has been shown in selected patients, but larger studies are needed to confirm its safety and clinical role [329].

7.1.3.2.2 Open versus robotic approach

One study prospectively compared the peri-operative outcomes of a series of robot-assisted and open PN performed by the same experienced surgeon. Robot-assisted PN was superior to open PN in terms of lower estimated blood loss and shorter hospital stay. Warm ischaemia time, operative time, immediate- early- and short-term complications, variation in creatinine levels and pathologic margins were similar between groups [330].

A multicentre French prospective database compared the outcomes of 1,800 patients who underwent open PN and robot-assisted PN. Although the follow-up was shorter, there was a decreased morbidity in the robot-assisted PN group with less overall complications, less major complications, less transfusions and a much shorter hospital stay [331].

A SR and meta-analysis comparing RAPN and OPN demonstrated similar short-term functional outcomes, however results are inconsistent [332].

OPERA, a prospective RCT comparing open (OPN) vs. robotic partial nephrectomy (RAPN) in intermediate/high complexity renal tumours (RENAL Score > = 7) prematurely closed due to poor accrual and data have not been fully published [333].

The single-centre, open-label feasibility ROBOCOP II RCT enrolled patients with suspected localised RCC referred for PN and randomised them at a 1:1 ratio to either RAPN or OPN [334]. The primary outcome was the feasibility of recruitment, assessed as the accrual rate. Secondary outcomes included perioperative and post-operative data. Overall, 50 patients underwent RAPN or OPN (accrual rate 65%). In comparison to OPN, RAPN had lower blood loss, less need for opioids, and fewer complications according to the mean Comprehensive Complication Index. OPN has a shorter operative time and warm ischemia time. There were no differences between RAPN and OPN regarding post-operative functional outcomes. Considering the limitations of both prospective trials, the clinical impact of robotic PN is still controversial.

7.1.3.2.3 Open versus hand-assisted approach

Hand-assisted laparoscopic PN (HALPN) is rarely performed. A comparative study of open vs. HALPN showed no difference in OS or RFS at intermediate-term follow-up. The authors observed a lower rate of intra-operative and all-grade post-operative 30-day complications in HALPN vs. open PN patients, but there was no significant difference in high Clavien grade complications. Three months after the operation, GFR was lower in the HALPN than in the open PN group [335].

7.1.3.2.4 Open versus laparoscopic versus robotic approaches

In a retrospective propensity-score-matched study, comparing open-, laparoscopic- and robot-assisted PN, after five years of median follow-up, similar rates of local recurrence, distant metastasis and cancer-related death rates were found [336].

7.1.3.2.5 Laparoscopic versus robotic approach

Another study included the 50 last patients having undergone laparoscopic and robotic PN for T1-T2 renal tumours by two different surgeons with an experience of over 200 procedures each in laparoscopic and robotic PN and RAPN, respectively, at the beginning of the study. Peri-operative and short-term oncological and functional outcomes appeared broadly comparable between RAPN and LPN when performed by highly experienced surgeons [337].

A meta-analysis, including a series of NSS with variable methodological quality compared the peri-operative outcomes of robot-assisted- and laparoscopic PN. The robotic group had a significantly lower rate of conversion to open surgery and to radical surgery, shorter warm ischaemia time, smaller change in estimated GFR after surgery and shorter length of hospital stay. No significant differences were observed between the two groups regarding complications, change of serum creatinine after surgery, operative time, estimated blood loss and positive surgical margins (PSMs) [338].

A multi-institutional prospective study of 105 patients with hilar tumours demonstrated a reduced warm ischaemia time (20.2 min vs. 27.7 min) and a comparable rate of 1.9% when compared with a historical laparoscopic control group which was defined by literature research and meta-analysis for warm ischaemia time and PSM, respectively [339].

7.1.3.2.6 Laparoscopic transperitoneal versus retroperitoneal approach

Data from the Italian RECORD 2 project, a multi-institutional prospective observational project, compared the transperitoneal vs. the retroperitoneal approach for laparoscopic PN. After propensity score matching (each group n = 413) no differences in post-operative complications (surgical and medical), PSMs, early and late eGFR levels were observed. Intra-operative and surgical complications were slightly higher and operative times lower in the transperitoneal vs. the retroperitoneal approach [340]. In terms of peri-operative complications, retroperitoneal and transperitoneal PN have similar outcomes [327].

A SR assessed the outcomes of retroperitoneal vs. transperitoneal RAPN. Seventeen studies, published between 2013 and 2021, were retrieved; none of which an RCT. Among the 6,266 patients included 2,261 (36.1%) and 4,005 (63.9%) underwent retroperitoneal vs. transperitoneal RAPN, respectively. Both retroperitoneal and transperitoneal RAPN offered similar surgical outcomes, while retroperitoneal RAPN was associated with shorter surgical time and length of hospital stay [341].

7.1.3.2.7 Tumour enucleation, standard partial nephrectomy and single-port approach

Simple tumour enucleation also had similar PFS and CSS rates compared to standard PN and RN in a large study [328]. The feasibility of laparo-endoscopic single-site PN has been shown in selected patients but larger studies are needed to confirm its safety and clinical role [329].

The only prospective multi-centre study available to date assessing the impact of resection technique (enucleation vs. enucleoresection vs. resection) during PN using a standardised reporting score to classify the resection technique after surgery found that the resection technique significantly impacts surgical complications, early functional outcomes and positive surgical margins after PN of localised renal masses [342].

A SR and pooled analysis found heterogeneity in the reporting of resection techniques across robotic PN series [343]. Out of 20 studies retrieved, nine compared “standard” resection versus enucleation. A pooled analysis did not reveal significant differences in terms of operative time, ischemia time, blood loss, transfusions, or positive margins. Significant differences favoring enucleation were found for clamping management (odds ratio [OR] for renal artery clamping 3.51, 95% confidence interval [CI] 1.13-10.88; p = 0.03), overall complications (OR for occurrence 0.55, 95% CI 0.34-0.87; p = 0.01) major complications (OR for occurrence 0.39, 95% CI 0.19-0.79; p = 0.009), length of stay (weighted mean difference [WMD] -0.72 d, 95% CI -0.99 to -0.45; p < 0.001), and decrease in estimated glomerular filtration rate (WMD -2.64 ml/min, 95% CI -5.15 to -0.12; p = 0.04).

7.1.3.2.8 Off-clamp versus On-clamp PN

The use of a off-clamp and selective-clamping approaches for PN has increased in recent years with the aim to minimise/avoid warm ischemia time and improve functional outcomes. One RCT (CLOCK study) showed a comparable safety profile of off-clamp vs. on-clamp PN in terms of intra- and peri-operative complications as well as comparable absolute eGFR variation and split renal function at 6 months from surgery in patients with regular baseline function and two kidneys. However, 40% of the patients randomised in the off-clamp group, were intraoperatively shifted to on-clamp (median ischemia time of 15 minutes) [344, 345]. Due to the selective

inclusion criteria of the RCT, off-clamp techniques may still be indicated in patients with chronic kidney disease, single kidney or multifocal disease [346, 347].

In a contemporary cohort of 1359 patients from the prospectively maintained database of the French national network of research on kidney cancer (UROCCR), PSM rate was not statistically different between the off-clamp group (5.6%) and the on-clamp group (11%) (p = 0.1). With short median follow-up, no statistical differences between the two groups were seen in OS, local RFS and metastasis-free survival (MFS) [348].

7.1.3.2.9 Surgical volume

In a analysis of 8,753 patients who underwent PN, an inverse non-linear relationship of hospital volume with morbidity of PN was observed, with a plateauing seen at 35-40 cases per year overall, and 18-20 cases for the robotic approach [349]. A retrospective study of a U.S. National Cancer Database looked at the prognostic impact of hospital volume and the outcomes of robot-assisted PN, including 18,724 cases. This study showed that undergoing RAPN at higher-volume hospitals may have better peri-operative outcomes (conversion to open and length of hospital stay) and lower PSM rates [350]. A French study, including 1,222 RAPN patients, has shown that hospital volume is the main predictive factor of Trifecta achievement (no complications, warm ischaemia time < 25 min, and negative surgical margins) after adjustment for other variables, including surgeon volume [351]. The prospective Registry of Conservative and Radical Surgery for cortical renal tumour Disease (RECORd-2) study including 2,076 patients showed that the hospital volume (> 60 PN/year) is an independent predictor for PSMs [352].

7.1.3.2.10 Pre-operative embolisation prior to partial nephrectomy

A SR and meta-analysis of 270 patients demonstrated significantly reduced blood loss in patients with selective renal artery embolisation (n = 222; 154 ± 22.6 mL vs. n = 48; 353.4 ± 69.6 mL) prior to PN [353].

7.1.3.3 Positive surgical margins on histopathological specimens

A PSM is encountered in about 2-8% of T1 PNs [354]. Studies comparing surgical margins with different surgical approaches (open, laparoscopic, robotic) are inconclusive [355-357]. Most trials showed that intra-operative frozen section analysis had no influence on the risk of definite PSMs [358]. A PSM status occurs more frequently in cases in which surgery is imperative (solitary kidneys and bilateral tumours) and in patients with adverse pathological features (pT2a, pT3a, grade III–IV) [359-362].

The majority of retrospective analyses reported so far indicated that PSMs do not translate into a higher risk of metastases or a decreased CSS [360, 361]. On the other hand, another retrospective study of a large single-institutional series showed that PSMs are an independent predictor of PFS due to a higher incidence of distant and local relapses [363]. Another retrospective study of 42,114 PN patients with 2,823 PSM patients (6.7%) showed an increased presence of PSM in upstaged pT3a tumours (14.1%), increased all-cause mortality in PSM patients and a decreased 5-year OS rate in pT3a tumours (PSM: 69% vs. NSM: 90.9 %) [364].

However, only a proportion of patients with an uncertain margin status actually harbour residual malignancy. Local tumour bed recurrences were found in 16% in patients with PSMs compared with 3% in those with negative margins [359], Therefore, RN or re-resection of margins can result in over-treatment in many cases. Patients with PSMs should be informed that they will need a more intense surveillance (imaging) follow-up and that they are at increased risk of secondary local therapies [360, 365]. On the other hand, protection from recurrence is not ensured by negative surgical margins [366] as it is reported in up to 1.5% of cases in this category of patients [354].

7.1.3.4 Summary of evidence and recommendations for radical and partial nephrectomy techniques

Summary of evidence	**LE**
Laparoscopic RN has lower morbidity than open nephrectomy.	1b
Short-term oncological outcomes for T1-T2a tumours are equivalent for laparoscopic- and open RN.	2a
Partial nephrectomy can be performed, either by open-, pure laparoscopic- or robot-assisted approach, based on surgeon's expertise and skills.	2b
Robot-assisted and laparoscopic PN are associated with shorter length of hospital stay and lower blood loss compared to open PN.	2b

Transperitoneal and retroperitoneal laparoscopic PN do not differ in post-operative surgical and medical complications, PSMs, and kidney function.	2a
Hospital volume for PN might impact on surgical complications, warm ischaemia time and surgical margins.	3
Immediate completion nephrectomy for PSMs can result in over-treatment in many cases.	3
Off-clamp partial nephrectomy does not improve renal function outcomes in patients with baseline normal renal function.	1b

Recommendations	**Strength rating**
Offer laparoscopic or robotic radical nephrectomy (RN) to patients with T2 tumours and localised masses not treatable by partial nephrectomy (PN).	Strong
Do not perform minimally invasive RN in patients with T1 tumours for whom a PN is feasible by any approach, including open.	Strong
Do not perform minimally invasive surgery if this approach may compromise oncological-functional- and peri-operative outcomes.	Strong
Intensify follow-up in patients with a positive surgical margin, especially in upstaged pT3a patients.	Weak
Do not attempt off-clamp partial nephrectomy unless indicated.	Weak

*7.1.4 **Therapeutic approaches as alternatives to surgery***

7.1.4.1 Active surveillance and watchful waiting

Elderly and comorbid patients with incidental SRMs have a low RCC-specific mortality and significant competing-cause mortality [367, 368].

In this regard, beyond age and comorbidities, frailty has been increasingly recognised as a major risk factor for adverse perioperative and oncological outcomes in patients with genitourinary malignancies. Frailty is a geriatric syndrome characterised by a decline in individuals' resilience and physiological functional reserve across multiple body systems, resulting in increased vulnerability to external stressors [369]. The Comprehensive Geriatric Assessment is considered the gold standard of care for older patients in several settings, given its ability to identify frailty and risk of geriatric syndromes and the positive impact on patients' outcomes.

A SR evaluatig the impact of frailty on perioperative and oncologic outcomes in patients undergoing surgery or ablation for RCC found low-quality evidence pointing to frailty and sarcopenia as potential independent risk factors for worse perioperative and oncological outcomes across different RCC stages.

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 [370]. The concept of AS differs from the concept of 'Watchful Waiting'; Watchful Waiting is reserved for patients whose comorbidities contra-indicate any subsequent active treatment and who do not require follow-up imaging, unless clinically indicated.

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 CSM in patients treated with surgery [281, 371, 372]. However, the patients assigned to the surveillance arm were older and likely to be frailer and less suitable for surgery. Other-cause mortality rates in the non-surgical group significantly exceeded that of the surgical group [371]. Analyses of older patients (> 75 years) failed to show the same benefit in CSM for surgical treatment [280, 373, 374].

Growth rate and metastasis

In the largest reported series of AS the growth of renal tumours was low and progression to metastatic disease was reported in only a limited number of patients [375, 376]. A SR of eighteen AS cohorts comprising 2,066 patients (cT1-2 N0M0) with a pooled mean follow-up of 53 months, showed that 2.1% (95% CI: 1.0-3.6) of patients developed metastatic disease during follow-up [377]. For patients with SRMs (nine studies, n = 987), the pooled metastasis rate was 1.8% (95% CI: 0.5-3.7).

In 136 biopsy-proven SRMs managed by AS, median follow-up of patients who remained on AS was 5.8 years (interquartile range 3.4-7.5 years). Clear-cell RCC grew faster than papillary type 1 SRMs (0.25 and 0.02 cm/year on average, respectively, p = 0.0003). Overall, 60 (44.1 %) of the malignant SRMs progressed; 49 (82%) by rapid growth (volume doubling), seven (12%) increasing to ≥ 4 cm, and four (6.7%) by both criteria. Six patients developed metastases, and all were of ccRCC histology [378].

Overall- and cancer-specific survival

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, at multivariate analysis, management type was not associated with OS after adjusting for age, comorbidities, and other variables [367]. No statistically significant differences in OS and CSS were observed in another study of RN vs. PN vs. AS for T1a renal masses with a follow-up of 34 months [379].

The prospective non-randomised multi-institutional Delayed Intervention and Surveillance for Small Renal Masses (DISSRM) study enrolled 497 patients with solid renal masses < 4 cm who selected either AS or primary active intervention. Patients who selected AS were older, had worse ECOG scores, more comorbidities, smaller tumours, and more often had multiple and bilateral lesions. In patients who elected AS in this study the overall median SRM growth rate was 0.09 cm/year with a median follow-up of 1.83 years. The growth rate and variability decreased with longer follow-up. No patients developed metastatic disease or died of RCC [380, 381].

Overall survival for primary intervention and AS was 98% and 96% at two years, and 92% and 75% at five years, respectively (p = 0.06). At five years, CSS was 99% and 100%, respectively (p = 0.3). Active surveillance was not predictive of OS or CSS in regression modelling with relatively short follow-up [380]. In the previously mentioned large SR of eighteen AS cohorts 1.0% (95% CI: 0.3-2.1) died from RCC and 22.6% (95% CI: 15.8-30.2) died from any cause. For patients with SRMs RCC-specific mortality was 0.6% (95% CI: 0-2.1), and all-cause mortality was 28.5% (95% CI: 17.4-41.4) [377].

A study using data from the DISSRM Registry investigated the outcomes of active surveillance in a cohort of patients aged 60 or younger at diagnosis [382]. Of 224 patients with median follow-up of 4.9 years, 30.4% chose surveillance. There were 20 (29.4%) surveillance progression events, including four elective crossovers, and 13 (19.1%) patients underwent delayed intervention. Among patients with initial tumour size ≤ 2 cm, 15.1% crossed over, compared to 33.3% with initial tumour size 2-4 cm. Overall survival was similar in primary intervention and surveillance at 7 years (94.0% vs 90.8%, log-rank p = 0.2). Cancer-specific survival remained at 100% for both groups. Recurrence-free survival at five years was 96.0% and 100% for primary and delayed intervention, respectively (log-rank p = 0.6).

Overall, both short- and intermediate-term oncological outcomes indicate that in selected patients with advanced age and/or comorbidities, AS is appropriate for initially monitoring of SRMs, followed, if required, by treatment for progression [370, 375, 376, 383-386].

Quality of life

A multicentre study assessed QoL of patients undergoing immediate intervention vs. AS. Patients undergoing immediate intervention had higher QoL scores at baseline, specifically for physical health. The perceived benefit in physical health persisted for at least one year following intervention. Mental health, which includes domains of depression and anxiety, was not adversely affected while on AS [387].

7.1.4.2 Role of renal tumour biopsy before active surveillance

Histological characterisation of SRMs by renal tumour biopsy is useful to select tumours at lower risk of progression based on grade and histotype, which can be safely managed with AS. Pathology can also help to tailor surveillance imaging schedules. In the largest cohort of biopsy-proven, small, sporadic RCCs followed with AS, a significant difference in growth and progression among different RCC subtypes was observed. Clear-cell RCC SRMs grew faster than papillary type 1 SRMs (0.25 and 0.02 cm/year on average, respectively, p = 0.0003) [378].

7.1.4.3 Tumour ablation

7.1.4.3.1 Role of renal mass biopsy

A RMB is required prior to tumour ablation (see Sections 5.3 - Renal tumour biopsy and 5.4 - Summary of evidence and recommendations for the diagnostic assessment of RCC). Historically, up to 45% of patients underwent tumour ablation of a benign or non-diagnostic mass [388, 389]. An analysis of the European multi-national prospective EuRECA registry (871 patients undergoing cryoablation) showed that the use of pre-cryoablation biopsy has significantly increased from 42% (65/156) in 2015 to 72% (88/122) in 2019 (p < 0.001), making treatment for a benign or an unknown histology significantly less likely (OR: 0.64, p < 0.001 and OR 0.31, p = 0.044, respectively) [390]. A RMB in a separate session reduces over-treatment significantly, with 80% of patients with benign lesions opting not to proceed with TA [389]. Additionally, there is some evidence that the oncological outcome following TA differs according to RCC subtype which should therefore be factored into the decision-making process. In a series of 229 patients with cT1a tumours (mean size 2.5 cm) treated with RFA, the 5-year DFS rate was 90% for ccRCC and 100% for pRCC (80 months: 100% vs. 87%, p = 0.04) [391]. In another series, the total tumour ablation effectiveness rate was 90.9% for ccRCC and 100% for pRCC [392].

A study comparing RFA with surgery suggested worse outcomes of RFA vs. PN in cT1b ccRCC, while no difference was seen in those with non-ccRCC [393]. Furthermore, patients with high-grade RCC or metastasis may choose different treatments over tumour ablation. Finally, patients without biopsy or a non-diagnostic biopsy are often assumed to have RCC and will undergo potentially unnecessary radiological follow-up or further treatment.

7.1.4.3.2 Cryoablation

Cryoablation is performed using either a percutaneous- or a laparoscopic-assisted approach, with technical success rates of > 95% [394]. In comparative studies, there was no significant difference in the overall complication rates between laparoscopic- and percutaneous cryoablation [395-397]. One comparative study reported similar OS, CSS, and RFS in 145 laparoscopic patients with a longer follow-up vs. 118 patients treated percutaneously with a shorter follow-up [396]. A shorter average length of hospital stay was found with the percutaneous technique [396-398]. A SR including 82 articles reported complication rates ranging between 8-20% with most complications being minor [399]. Although a precise definition of tumour recurrence is lacking, the athors reported a lower RFS as compared to that of PN.

Oncological outcomes after cryoablation have generally been favourable for cT1a tumours. In a recently published series of 308 patients with cT1a and cT1b tumours undergoing percutaneous cryoablation, local recurrence was seen in 7.7% of cT1a tumours vs. 34.5% of cT1b tumours. On multivariable regression, the risk of disease progression increased by 32% with each 1 cm increase in tumour size (HR: 1.32, $p < 0.001$). Mean decline in eGFR was 11.7 mL/min/1.73 m2 [400]. In another large series of 220 patients with biopsy-proven cT1 RCC, five-year local RFS was 93.9%, while metastasis-free survival approached 94.4% [394]. A series of 134 patients with T1 RCC (median tumour size 2.8 cm) submitted to percutaneous cryoablation yielded a ten-year DSF of 94% [401].

For cT1b tumours, local tumour control rates drop significantly. One study showed local tumour control in only 60.3% at three years [402]. In another series, the PFS rate was 66.7% at twelve months [403]. Furthermore, recent analyses demonstrated five-year cancer-specific mortality rates of 7.6-9% [404, 405]. On multivariable analysis, cryoablation of cT1b tumours was associated a 2.5-fold increased risk of death from RCC compared with PN [404]

Recurrence after initial cryoablation is often managed with re-cryoablation, but only 45% of patients remain disease-free at two years [406].

7.1.4.3.3 Radiofrequency ablation

Radiofrequency ablation is performed laparoscopically or percutaneously. Several studies compared patients with cT1a tumours treated by laparoscopic or percutaneous RFA [407-410]. Complications occurred in up to 29% of patients but were mostly minor. Complication rates, recurrence rates and CSS were similar in patients treated laparoscopically and percutaneously.

The initial technical success rate on early (i.e., one month) imaging after one session of RFA is 94% for cT1a and 81% for cT1b tumours [411]. This is generally managed by re-RFA, approaching overall total technical success rates > 95% with one or more sessions [412].

Long-term outcomes with over five years of follow-up following RFA have been reported. In recent studies, the five-year OS rate was 73–79% [411, 412], due to patient selection. While oncological outcomes have been favourable for cT1a tumours, it's important to note that within the T1a 3-4cm subpopulation, these outcomes are less encouraging [413]. A study involving 106 patients treated with radiofrequency ablation, and with a median follow-up of 79 months, the ten-year DFS rate was 82%, but a notable decline was observed to 68% for tumours larger than 3 cm [412]. In series focusing on clinical T1b tumours (4.1–7.0 cm), the five-year DFS rate was 74.5% to 81% [411, 414]. Oncological outcomes appear to be worse than after surgery, but comparative data are severely biased (see Section 7.1.4.3.4). In general, most disease recurrences occur locally and recurrences beyond five years are rare [412, 414].

7.1.4.3.4 Microwave ablation

The best evidence base for these techniques exists for percutaneous microwave ablation. In a study of 185 patients with a median follow-up of 40 months, the five-year local progression rate was 3.2%, while 4.3% developed distant metastases [415]. Results appear to be favourable for cT1b tumours as well [416]. Overall, current data on cryoablation, RFA and microwave ablation of cT1a renal tumours indicate short-term equivalence with regards to complications, oncological and renal functional outcomes [417, 418].

7.1.4.3.5 Tumour ablation versus surgery

The Guideline Panel performed a protocol-driven SR of comparative studies (including > 50 patients) of TA with PN for T1N0M0 renal masses [419]. Twenty-six non-randomised comparative studies published between 2000 and 2019 were included, recruiting a total of 16,780 patients. Four studies compared laparoscopic TA vs.

laparoscopic/robotic PN; sixteen studies compared laparoscopic or percutaneous TA vs. open-, laparoscopic- or robotic PN; two studies compared different techniques of TA and four studies compared TA vs. PN vs. RN. In this SR, TA as treatment for T1 renal masses was found to be safe in terms of complications and adverse events (AEs), but its long-term oncological effectiveness compared with PN remained unclear. The primary reason for the persisting uncertainty was related to the nature of the available data; most studies were retrospective observational studies with poorly matched controls, or single- arm case series with short follow-up. Many studies were poorly described and lacked a clear comparator.

There was also considerable methodological heterogeneity. Another major limitation was the absence of clearly defined primary outcome measures. Even when a clear endpoint such as OS was reported, data were difficult to interpret because of the varying length and type of follow-up amongst studies. The Panel also appraised the published SRs based on the AMSTAR 2 tool which showed "Critically Low" or "Low" ratings [419].

Tumour ablation has been demonstrated to be associated with good long-term survival in several single-arm non-comparative studies [420, 421]. Due to the lack of controls, this apparent benefit is subject to significant uncertainties. Whether such benefit is due to the favourable natural history of such tumours or due to the therapeutic efficacy of TA, as compared to PN, remains unknown. In addition, there are data from comparative studies suggesting TA may be associated with worse oncological outcomes in terms of local recurrence and metastatic progression and CSM [279, 404, 405, 422-424]. However, there appears to be no clinically significant difference in five-year CSM between TA and AS [372]. A retrosepctive multicentre study, including 86 partial nephrectomies and 104 TA, matched for complexities, has shown that PN and cryoablation are comparable regarding complications within 90 days after treatment [425].

The Panel concluded that the current data are inadequate to reach conclusions regarding the clinical effectiveness of TA as compared with PN. Given these uncertainties in the presence of only low-quality evidence, TA can only be recommended to frail and/or comorbid patients with SRMs.

7.1.4.3.6 Stereotactic ablative radiotherapy

Stereotactic ablative radiotherapy (SABR) has been emerging as a treatment option for medically inoperable patients with localised cT1a and cT1b tumours [426, 427].

A variety of dose-fractionation schedules have been reported (26-60Gy; single, three and five fractions) [427]. Published single-arm studies, mainly including cT1 RCC, with a median follow-up range of 16.4-34.3 months, reported local control rates of 90-97.2% [427-434]. However, viable tumour cells are often seen in post-SABR biopsies, although their clinical significance remains unclear [430]. Grade 3 or 4 toxicities were reported in 0-9.1% of the patients across studies [427]. Even though early reported results of SABR look encouraging, more evidence from well conducted prospective studies with longer follow-up is needed.

7.1.4.3.7 Other ablative techniques

Some studies have shown the feasibility of other ablative techniques, such as high-intensity focused US ablation and non-thermal irreversible electroporation. However, these techniques are still considered experimental.

7.1.4.3.8 Summary of evidence and recommendations for therapeutic approaches as alternative to surgery

Summary of evidence	**LE**
Most population-based analyses show a significantly lower CSM for patients treated with surgery compared to non-surgical management.	3
In AS cohorts, the growth of SRMs is low in most cases and progression to metastatic disease is rare (1–2%).	3
Low quality studies suggest higher disease recurrence rates after RFA of tumours > 3 cm and after cryoablation of tumours > 4 cm.	3
Low quality studies suggest a higher local recurrence rate for TA therapies compared to PN, but quality of data does not allow definitive conclusions.	3

Recommendations	Strength rating
Offer active surveillance (AS) or tumour ablation (TA) to frail and/or comorbid patients with small renal masses.	Weak
Perform a percutaneous renal mass biopsy prior to, and not concomitantly with, TA.	Strong
When TA or AS are offered, discuss with patients about the harms/benefits with regards to oncological outcomes and complications.	Strong
Do not routinely offer TA for tumours > 3 cm and cryoablation for tumours > 4 cm.	Weak

7.2 Treatment of locally advanced RCC

*7.2.1 **Introduction***

In addition to the summary of evidence and recommendations outlined in Section 7.1 for localised RCC, certain therapeutic strategies arise in specific situations for locally-advanced disease.

*7.2.2 **Role of lymph node dissection in locally-advanced RCC***

In locally-advanced RCC, the role of LND is still controversial. The only available RCT demonstrated no survival benefit for patients undergoing LND but this trial mainly included organ-confined disease cases [293]. In the setting of locally-advanced disease, several retrospective papers and SRs addressed the topic with contradictory results. A SR and meta-analyses could not confirm any survival benefit in patients at high risk of progression treated with LND [435]. A More recent SR and meta-analyses showing a survival benefit in patients with locally-advanced disease treated with LND [436]. More specifically, thirteen studies on patients with LND and non-LND were identified and included in the analysis. In the subgroup of locally-advanced RCC (cT3-T4NxM0), LND showed a significantly better OS rate in patients who had undergone LND compared to those without LND (HR: 0.73, 95% CI: 0.60-0.90, p = 0.003).

7.2.2.1 Management of clinically negative lymph nodes (cN-) in locally-advanced RCC

In case of cN-, the probability of finding pathologically-confirmed LN metastases ranges between 0-25%, depending mainly on primary tumour size and the presence of distant metastases [437]. In case of clinically-negative LNs (cN-) at imaging, removal of LNs is justified only if visible or palpable during surgery [438], at least for staging, prognosis, adjuvant therapy and follow-up implications, although a benefit in terms of cancer control has not yet been demonstrated [295, 435].

7.2.2.2 Management of clinically positive lymph nodes (cN+) in locally-advanced RCC

In case of cN+, the probability to identify pathologically-confirmed LN metastases ranges between 10.3% (cT1 tumours) and up to 54.5% in case of locally-advanced disease. In cN+, removal of visible and palpable nodes during LND is justified [438], at least for staging, prognosis, adjuvant therapy and follow-up implications, although a benefit in terms of cancer control has not yet been demonstrated [295, 435]. Whether to extend the LND in case of lymphadenopathy (cN1) remains controversial. In addition retrospective data showed for resected isolated macrospcopical lympnode metastises (pN1) that the time to systemic progression was a median of 4.2 months [439].

*7.2.3 **Management of RCC with venous tumour thrombus***

Tumour thrombus formation in RCC patients is a significant adverse prognostic factor. Traditionally, patients with venous tumour thrombus undergo surgery to remove the kidney and tumour thrombus. Aggressive surgical resection is widely accepted as the default management option for patients with venous tumour thrombus [440-448].

The role of neoadjuvant treatment with targeted agents has also been investigated in downstaging of tumour thrombus within the inferior vena cava (IVC) with limited and controversial results [449, 450]. Further investigations are needed to better identifying which patients with RCC and tumour venous might benefit from neoadjuvant therapy (See also section 7.2.5).

Several scores and tools have been proposed to estimate surgical complexity and the risk of complications, although an external validation is needed [451, 452].

In two of the largest published studies a higher OS was different in patients with a level of thrombus in the renal vein and inferior caval vein and survival was also not associated with tumour size, grade, perinephric fat extension, sarcomatoid features, Eastern Cooperative Oncology Group PS and regional- and distant metastases in multivariate analysis [453, 454]. Therefore, all patients with non-metastatic disease and venous tumour thrombus, and an acceptable PS, should be considered for surgical intervention, irrespective of the extent of tumour thrombus at presentation.

The surgical technique (open vs. laparoscopic vs. robotic) and approach for each case should be selected based on patients' characteristics, surgeon and hospital volumes and the extent of tumour thrombus and the grade of occlusion of the IVC [449, 455, 456]. Minimally invasive techniques (laparoscopic and robotic) are still under investigation [457, 458].
A SR and metaanalyses regarding surgical approach included 1,375 patients, out of which 329 patients were in single-arm studies and 1,046 patients were in comparative studies [459]. Of the 329 patients who underwent robotic, 14.7% were level I, 60.9% level II, 20.4% level III and 2.5% level IV thrombus. Compared with open thrombectomy, robotic approach was associated with a lower blood transfusion rate and fewer overall complications. Major complication and 30-day mortality rates were similar in both groups. In experienced hands with carefully selected patients, robotic thrombectomy can be considered; however, an emphasised selection bias limits definitive inference of these results, and optimal patient selection criteria remain to be elucidated.

In case of venous thrombus, referral to a tertiary care centre is recommended to guarantee a multidisciplinary evaluation and treatment, especially in case of caval thrombus.

*7.2.4 **Management of locally-advanced unresectable RCC***

The management of locally-advanced unresectable RCC should be based around systemic therapy [460]. A multidisciplinary evaluation, including urologists, medical oncologists and radiation therapists is suggested to maximise cancer control, pain control and the best supportive care. In patients with non-resectable disease, embolisation can control symptoms, including visible haematuria or flank pain [309, 461-463].

7.2.4.1 Summary of evidence and recommendations for lymph node dissection, the management of RCC with venous tumour thrombus and unresectable tumours

Summary of evidence	**LE**
In patients with locally-advanced disease, the survival benefit of LN dissection is unproven but LN dissection has significant staging, prognosis, adjuvant therapy and follow-up implications.	3
Low quality data suggest that tumour thrombus excision in non-metastatic disease may be beneficial.	3

Recommendations	**Strength rating**
During nephrectomy, remove clinically enlarged lymph nodes for staging, prognosis and follow-up implications.	Weak
Remove the renal tumour and thrombus in case of venous involvement in non-metastatic disease.	Strong
Discuss treatment options in patients with locally-advanced unresectable RCC (biopsy and/or systemic therapy/deferred resection, or palliative management) within a multidisciplinary team to determine treatment goal.	Strong

*7.2.5 **Neoadjuvant and adjuvant therapy***

Neoadjuvant therapy is currently under investigation and available in clinical trials. In the pre-surgical setting neoadjuvant TKI and immune checkpoint therapy demonstrated varying response rates between 7-59% in retrospective series and some phase II trials [449, 464, 465].

In a presurgical phase II trial in patients with vascular thrombus treatment with axitinib demonstrated a reduction in the level of tumour thrombus in 35% of patients (7/20) [464]. There is currently no evidence of a prolonged OS by neoadjuvant treatment and at present, the data do not support its use outside clinical trials.

There is currently no evidence from a SR (including ten retrospective studies and two RCTs) that adjuvant radiation therapy increases survival [466]. The impact on OS of adjuvant tumour vaccination in selected patients undergoing nephrectomy for T3 renal carcinomas remains unconfirmed [467-471] (LE: 1b). A similar observation was made in an adjuvant trial of girentuximab, a monoclonal antibody against carbonic anhydrase IX (CAIX) (ARISER Study) [472].

At present, there is no OS data supporting the use of adjuvant VEGFR or mTOR inhibitors. Thus far, several RCTs comparing VEGFR-TKI or mTOR vs. placebo have been published [473-481]. Only S-TRAC, a trial of adjuvant sunitinib vs. placebo demonstrated a DFS benefit which was not reproduced in ASSURE, a trial of sunitinib and sorafenib vs. placebo. Due to an unfavourable AE profile and no survival advantage, none of these drugs are recommended [482].

7.2.5.1 PD-1 Inhibition: Keynote-564

The Keynote-564 trial is the first trial to report positive primary endpoint data on DFS [483, 484]. Keynote-564 evaluated pembrolizumab (17 cycles of 3-weekly therapy) vs. placebo as adjuvant therapy in 994 patients with intermediate (pT2, grade 4 or sarcomatoid, N0, M0; or pT3, any grade, N0, M0) or high risk (pT4, any grade, N0, M0; or pT any stage, and grade, or N+, M0), or M1 (no evidence of disease [NED] after primary tumour plus soft tissue metastases completely resected < one year from nephrectomy) disease. The median follow-up, defined as time from randomisation to data cut-off, was 24.1 months. The primary endpoint of DFS per investigator assessment was significantly improved in the pembrolizumab group vs. placebo (HR: 0.68, 95% CI: 0.53–0.87, p = 0.001). The estimated 24-month DFS rate was 77% vs. 68% for pembrolizumab and placebo, respectively. Benefit occurred across broad subgroups of patients including those with M1/NED disease post-surgery (n = 58 [6%]). Investigator assessed DFS was considered preferable to DFS by central review due to its clinical applicability. Overall survival showed a non-statistically significant trend towards a benefit in the pembrolizumab arm (HR: 0.54, 95% CI: 0.30-0.96, p = 0.0164). Follow-up was short and few OS events occurred (2-year OS rate of 97% [pembrolizumab] vs. 94% [placebo]). Grade III-V all-cause AEs occurred in 32% vs. 18% of patients for pembrolizumab and placebo, respectively. Quality of life assessment by FKSI-DRS and QLQ30 did not show a statistically significant or clinically meaningful deterioration in health-related QoL or symptom scores for either adjuvant pembrolizumab or placebo.

7.2.5.2 PD-L1 inhibition: IMmotion010

The IMmotion010 phase III trial was the first adjuvant ICI trial to be developed in RCC to investigate the effect of a PD-L1 inhibitor on DFS [485]. IMmotion010 evaluated atezolizumab 1200 mg (once every 3 weeks for 16 cycles or one year) vs. placebo as adjuvant therapy in 778 patients with increased risk of recurrence defined as: pT2, grade 4 or sarcomatoid, N0, M0; or pT3, grade 3–4, N0, M0; or pT3b/c/T4, any grade, N0, M0; or pT any stage and grade, pN1, M0, or M1 no NED after primary tumour plus soft tissue metastases completely resected either synchronous or if metachronous, > 12 months from nephrectomy.

The minimum follow-up, defined as time from randomisation to data cut-off, was 38.6 months. The primary endpoint of DFS per investigator assessment was not met in the atezolizumab group vs. placebo (HR: 0.93, 95% CI: 0.75-1.15, p = 0.4950) with a median DFS of 57.2 months (95% CI: 44.6, NE) for atezolizumab vs. 49.5 months for placebo (47.4, NE). None of the exploratory subgroups suggested a DFS benefit with atezolizumab, most notably the M1 NED subgroup (n = 108/13.9%) which was larger than in Keynote-564 (5.8%), the sarcomatoid subgroup and the subgroup expressing > 1% PD-L1 had a HR of 0.93 (0.58–1.49), 0.77 (0.44–1.36) and 0.83 (0.63-1.10), respectively.

There were no OS differences. Grade 3-4 all-cause and treatment-related AEs occurred in 27.2% and 14.1% vs. 21.1% and 4.7% of patients for atezolizumab and placebo, respectively. There were no treatment-related grade 5 AEs.

7.2.5.3 PD-1 and CTLA-4 inhibition: CheckMate 914

CheckMate 914 was the first phase III trial to investigate a combination of nivolumab plus ipilimumab vs. placebo as adjuvant treatment in RCC (part A) [486]. Subsequently, a nivolumab monotherapy arm was also added to the trial (part B). The following results relate to part A which evaluated nivolumab 240 mg every two weeks (Q2W) for 12 cycles or 6 months plus ipilimumab 1 mg/kg Q6W for 4 cycles vs. placebo in 816 patients with recurrence risk defined as pT2a, grade 3 or 4, N0, M0; pT2b/T3/T4, any grade, N0, M0, or pT any stage, any grade, pN1, M0. The median time of follow-up, defined as time from randomisation to data cut-off, was 37 months. The primary endpoint of DFS per investigator assessment was not met in the nivolumab plus ipilimumab group vs. placebo (HR 0.92 [0.71-1.19], p = 0.5347). Of the exploratory subgroups, patients with sarcomatoid tumours (n = 40) and those with > 1% PD-L1 expression (n = 107) had a HR of 0.29 (0.09-0.91) and 0.46 (0.23-0.94) in favour of the ICI combination, respectively.

All-cause treatment discontinuation due to study drug occurred in 43% and 33% in the nivolumab plus ipilimumab group vs. 11% and 1% in the placebo group. Treatment-related AE grade > III were 29% in the nivolumab plus ipilimumab group and 2% in the placebo group with four deaths (1%) considered related to combination therapy. The high AE profile may have contributed to the lack of efficacy and patient retention. The results of the nivolumab arm are awaited.

7.2.5.4 Perioperative PD-1 inhibition: PROSPER

PROSPER is a peri-operative trial of neoadjuvant nivolumab (one cycle) followed by radical or partial nephrectomy and adjuvant nivolumab (480 mg IV q4 weeks) for nine doses compared to surgery followed by surveillance without a placebo [487]. Patients with clinical stage > T2 or T any N+ RCC or patients with selected oligometastatic disease were included if they had no evidence of disease within 12-weeks post- surgery. A total of 819 patients with clear cell (87%) and non-ccRCC were included, a biopsy in the nivolumab arm was mandatory. The primary endpoint of RFS was similar between the arms (HR: 0.97; 95% CI: 0.74-1.28; p = 0.43)

and the trial was stopped by DSMC. The OS was not statistically different (HR: 1.48; 95% CI: 0.89-2.48; p = 0.93), although not mature. Grade III-IV AEs occurred in 20% (nivolumab arm) and 6% (control arm) of patients, respectively. Fifteen (4%) patients died in the nivolumab arm and eighteen (4%) in the surgery alone arm.

Following the application of the EAU Guidelines metodology, the Panel reached consensus and issued a weak recommendation for adjuvant pembrolizumab for patients with high-risk (defined as per study) operable ccRCC until final OS data are available [488]. This decision was taken as immune checkpoint inhibitor therapy has a different mode of action than VEGFR-TKI resulting in complete responses in up to 16% of patients in PD-1 unselected populations in metastatic disease [489]. Despite immature OS data with the early OS signal potentially driven by the M1 population the Panel cannot exclude that a survival benefit will emerge. This was not the case in the adjuvant sunitinib trial (STRAC) [486, 490]. The Panel took the following evidence limitations into account when deciding to make to a weak recommendation for adjuvant pembrolizumab:

- A high proportion of patients, cured by surgery, are receiving unnecessary, and potentially harmful treatment.
- The tolerability profile is acceptable but grade III-V AEs were higher with 14.7% in the pembrolizumab arm vs. the placebo arm (occurring in approximately one-third of patients, all cause). Approximately 18% of patients required treatment discontinuation early for AEs which gives a broad indicator of tolerability. There is a significant risk of life-changing toxicity.
- Other ICI trials have not shown consistent results.
- Biomarker analysis to predict outcome and AEs are not available.
- Final OS data are not yet available.

The results of IMmotion010, CheckMate 914 and PROSPER need to be discussed with patients [485-487]. Meta-analysis with these data sets is not recommended due to heterogeneity across the ICI studies. It is likely that there are several reasons behind these inconsistent results, including study population with potential heterogeneity independent of TNM risk groups, selection criteria and trial design. To date pembrolizumab is the only positive trial [490].

While the results of IMmotion010 may reflect the non-significant OS results seen in the metastatic setting with PD-L1 inhibitors (IMmotion151, Javelin 101), the results of CheckMate 914 and PROSPER are more difficult to interpret. Nivolumab and ipilimumab leads to durable remission and long-term OS in metastatic disease and nivolumab has a similar mode of action as pembrolizumab (anti PD-1).

The high treatment discontinuation rate of 33% in CheckMate 914 is of concern and may have had an impact on the trial effectivity (20% in Keynote-564). The Panel strongly feels that biomarker work on all of these trials should occur to identify patients that do respond to therapy and to give a better explanation for the inconsistent results. Treatment of unselected patients in the adjuvant setting based on the Keynote-564 criteria will result in a large proportion of patients receiving unnecessary therapy. In the absence of OS data or appropriate biomarkers, the patient preference should be leading in a shared decision-making process. Patients considering adjuvant therapy should be aware of all trials and not be presented with only one data set.

Table 7.1: Overview phase III trials of PD-1 immune checkpoint inhibitors in adjuvant RCC

Phase III trial of PD-1 immune checkpoint inhibitors in adjuvant RCC						
Study	**N**	**Experimental arm**	**Primary endpoint**	**Risk groups**	**DFS (mo) Median (95% CI) HR**	**OS (mo.) Median (95% CI) HR**
Keynote-564 NCT03142334 Median follow-up of 30.1 mo. [483]	994	PEMBRO 200 mg IV Q3W (17 cycles) vs. placebo	DFS in the ITT by IR	**Intermediate-high:** pT2 grade 4 or sarcomatoid; pT3 any grade **High:** pT4 any grade, pN1 **M1 NED:** cM0 after resection of oligometastatic disease < 12 mo.	(ITT) PEMBRO: NR (NE) PLACEBO: NR (NE) HR: 0.63 (95% CI: 0.50-0.80)) P < 0.002 DFS at 24 mo.: PEMBRO: 78.3% PLACEBO: 67.3%	(ITT) PEMBRO: NR (NE) PLACEBO: NR (NE) HR: 0.52 (95% CI: 0.31-0.86) not significant alive at 30 mo.: PEMBRO: 95.7% PLACEBO: 91.4%

IMmotion010 **NCT03024996** Median follow-up of 44.7 mo. [485]	778	ATEZO 1200 mg IV Q3W (16 cycles or 1 yr.) vs. placebo	DFS in the ITT by IR	**By TNM:** pT2 grade 4 or sarcomatoid; pT3 a grade 3-4; pT3b/c/T4 any grade, pN1 M1 NED: cM0 after resection of oligometastatic disease (synchronous or >/=12 mo.)	(ITT) ATEZO: 57.2 (44.6-NE) PLACEBO: 49.5 (47.4-NE) HR: 0.93 (95% CI: 0.75-1.15) p = 0.4950 DFS at 24 mo.: NR	(ITT) ATEZO : NE (59.8-NE) PLACEBO : NE (NE-NE) HR : 0.97 (95% CI: 0.67-1.42) alive at 24 mo.: NR
CheckMate 914 **NCT03138512** Median follow-up of 37.0 mo.[486]	816	NIVO 240 mg IV Q2W (× 12 cycles) + ipilimumab 1 mg/kg IV Q6W (× 4 cycles vs. placebo)	DFS in the ITT by BICR	**By TNM:** pT2a grade 3-4; pT2b/T3/T4 any grade, pN1	(ITT) NIVO + IPI: NR (NE) PLACEBO: 50.7 (48.1-NE) HR: 0.92 (95% CI: 0.71-1.19) p = 0.5347 DFS at 24 mo.: NIVO + IPI: 76.4% PLACEBO: 74.0%	NR
PROSPER **NCT03055013** Median follow-up: NR [487]	779	Neoadjuvant NIVO 240 mg IV Q2W (x 2 cycles) followed by adjuvant nivolumab 240 mg Q2W for 3 mo. and Q4W for 6 mo. vs. observation	RFS in the ITT by IR	**By TNM:** >/= cT2 (7 cm) or cT any cN1	(ITT), RFS: NIVO: NR (NE) Observation: NR (NE) HR: 0.97 (95% CI: 0.74-1.28) p = 0.43	(ITT) NIVO : NR (NE) Observation : NR (NE) HR: 1.48 (95% CI: 0.89-2.48) p = 0.93

ATEZO = atezolizumab; BICR = blinded independent central review; CI = confidence interval; DFS = disease-free survival; HR = hazard ratio; IPI = ipilimumab; IR = investigator review; ITT = intention-to-treat; IV = intravenous; mo = months; NE = non-estimable; NED = no evidence of disease; NIVO = nivolumab; NR = not reached; OS = overall survival; PD-1 = programmed death-receptor 1; PEMBRO = pembrolizumab; PFS = progressionfree survival; Q2W = every 2 weeks; Q3W = every 3 weeks.

7.2.5.5 Summary of evidence and recommendations for neoadjuvant and adjuvant therapy

Summary of evidence	**LE**
Neoadjuvant systemic therapy can reduce vascular thrombus and tumour size in the presurgical setting.	2a
Adjuvant sorafenib, pazopanib, everolimus, girentuximab, or axitinib does not improve DFS or OS after nephrectomy.	1b
In one single RCT, in selected high-risk patients, adjuvant sunitinib improved DFS but not OS.	1b
Adjuvant pembrolizumab defined by the inclusion criteria of the trial* after nephrectomy improves DFS.	1b
Adjuvant PD-L1 inhibition with atezolizumab did not improve DFS or OS.	1b
Adjuvant dual PD-1 and CTLA-4 inhibition with nivolumab and ipilimumab did not improve DFS.	1b
Peri-operative treatment with nivolumab did not improve RFS.	1b
The lack of biomarker data is hindering progress in this field. Adjuvant RCTs are ongoing to evaluate the benefit of adjuvant immunotherapy after nephrectomy in high-risk patients.	4

** pT2 G4 or pT3 any G; pT4 any G; pN+ any G; M1, NED after resection of metastases.*

Recommendations	Strength rating
Do not use neoadjuvant therapy outside a clinical trial setting.	Weak
Discuss the contradictory results of the available adjuvant ICI trials with patients to facilitate shared decision making.	Strong
Inform patients about the potential risk of overtreatment and immune related side effects if adjuvant therapy is considered.	Strong
Do not offer adjuvant therapy with sorafenib, pazopanib, everolimus, girentuximab, or axitinib.	Strong
Do not offer adjuvant sunitinib following surgically resected high-risk clear-cell renal cell carcinoma (ccRCC).	Weak

Offer adjuvant pembrolizumab to ccRCC patients, preferably within 12-16 weeks post-nephrectomy, with a recurrence risk as defined in the Keynote-564 trial:
• Intermediate-high risk:
  • pT2, grade 4 or sarcomatoid, N0 M0
  • pT3, any grade, N0, M0
• High risk:
  • pT4, any grade, N0, M0
  • any pT, any grade, N+, M0
• M1 no evidence of disease (NED):
  • NED after resection of oligometastatic sites ≤ 1 year from nephrectomy
	Weak

7.3 Advanced/metastatic RCC

*7.3.1 **Local therapy of advanced/metastatic RCC***

7.3.1.1 Cytoreductive nephrectomy

Tumour resection is potentially curative only if all tumour deposits are excised. This includes patients with the primary tumour in place and single- or oligometastatic resectable disease. For most patients with metastatic disease, cytoreductive nephrectomy (CN) is palliative and systemic treatments are necessary. In a combined analysis of two RCTs comparing CN+ IFN-based immunotherapy vs. IFN-based immunotherapy only, increased long-term survival was found in patients treated with CN [491]. However, IFN-based immunotherapy is no longer relevant in contemporary clinical practice.

Two RCTs [438, 492] and a narrative SR were identified [493]. The narrative SR included both RCTs and 10 non-RCTs. CARMENA, a phase III non-inferiority RCT investigating immediate CN followed by sunitinib vs. sunitinib alone, showed that sunitinib alone was not inferior to CN followed by sunitinib with regard to OS [494]. The trial included 450 patients with metastatic ccRCC of intermediate- and MSKCC poor risk of whom 226 were randomised to immediate CN followed by sunitinib and 224 to sunitinib alone. Patients in both arms had a median of two metastatic sites. Patients in both arms had a tumour burden of a median/mean of 140 mL of measurable disease by Response Evaluation Criteria In Solid Tumours (RECIST) 1.1, of which 80 mL accounted for the primary tumour. The study did not reach the full accrual of 576 patients and the Independent Data Monitoring Commission (IDMC) advised the trial steering committee to close the study. In an ITT analysis after a median follow-up of 50.9 months, median OS with CN was 13.9 months vs. 18.4 months with sunitinib alone (HR: 0.89, 95% CI: 0.71-1.10). This was found in both risk groups. For MSKCC intermediate-risk patients (n = 256) median OS was 19.0 months with CN and 23.4 months with sunitinib alone (HR: 0.92, 95% CI: 0.60-1.24) and for MSKCC poor risk (n = 193) 10.2 months and 13.3 months, respectively (HR: 0.86, 95% CI: 0.62-1.17). Non-inferiority was also found in two per-protocol analyses accounting for patients in the CN arm who either did not undergo surgery (n = 16) or did not receive sunitinib (n = 40), and patients in the sunitinib-only arm who did not receive the study drug (n = 11). Median PFS in the ITT population was 7.2 months with CN and 8.3 months with sunitinib alone (HR: 0.82, 95% CI: 0.67-1.00). The clinical benefit rate, defined as disease control beyond twelve weeks was 36.6% with CN and 47.9% with sunitinib alone (p = 0.022). Of note, 38 patients in the sunitinib-only arm required secondary CN due to acute symptoms or for complete or near-complete response. The median time from randomisation to secondary CN was 11.1 months.

The randomised EORTC SURTIME study revealed that the sequence of CN and sunitinib did not affect PFS (HR: 0.88, 95% CI: 0.59-1.37, p = 0.569). The trial accrued poorly and therefore results are mainly exploratory. However, in secondary endpoint analysis a strong OS benefit was observed in favour of the deferred CN approach in the ITT population with a median OS of 32.4 (range 14.5-65.3) months in the deferred CN arm vs. 15.0 (9.3-29.5) months in the immediate CN arm (HR: 0.57, 95% CI: 0.34-0.95, p = 0.032). The deferred CN approach appears to select patients with inherent resistance to systemic therapy [495]. This confirms

previous findings from single-arm phase II studies [493, 496]. Moreover, deferred CN and surgery appear safe after sunitinib which supports the findings, with some caution, of the only available RCT. In patients with poor PS or IMDC poor risk, small primaries, and high metastatic volume and/or a sarcomatoid tumour, CN is not recommended [497]. These data are confirmed by CARMENA [448] and upfront pre-surgical VEGFR-targeted therapy followed by CN seems to be beneficial [489].

Meanwhile first-line therapy recommendations for patients with their primary tumour in place have changed to ICI combination therapy (see Section 7.4.2.4) with sunitinib and other VEGFR-TKI monotherapies reserved for those who cannot tolerate ICI combination or have no access to these drugs. High-level evidence regarding CN is not available for ICI combinations but up to 30% of patients with primary metastatic disease, treated with their tumour in place, were included in the pivotal ICI combination trials (Table 7.2). The subgroup HRs, where available, suggest better outcomes for the ICI combination compared to sunitinib monotherapy. In mRCC patients without a need for immediate drug treatment, a SR evaluating effects of CN demonstrated an OS advantage of CN [493]. These data were supported by a nation-wide registry study showing that patients selected for primary CN had a significant OS advantage across all age groups [498].

Table 7.2: Key trials on immune checkpoint inhibitor combinations for primary metastatic disease

Trial	Drug combination	Number and % of patients treated with primary tumour in place	Number of patients treated with the primary tumour in place (ICI combination vs. sunitinib)		Subgroup analyses (HR with 95% CIs)	
			ICI combination	sunitinib	PFS	OS
CheckMate 214 [499]	ipilimumab + nivolumab	187/847 (22%)	84	103	NA	0.63 (0.42-0.94)
CheckMate 9ER [500]	cabozantinib + nivolumab	196/651 (30.1%)	101	95	0.63 (0.43-0.92)	0.79 (0.48-1.29)
Javelin 101 [501]	axitinib + avelumab	179/886 (20.2%)	90	89	0.75 (0.48-1.65)	NA
KEYNOTE-426 [502]	axitinib + pembrolizumab	143/861 (16.6%)	73	70	0.68 (0.45-1.03)	0.57 (0.36-0.89)
CLEAR [503]	lenvatinib + pembrolizumab	179/714 (25.1%)	97	82	0.38 (0.31-0.48)	0.52 (0.31-0.86)

CI = confidence interval; HR = hazard ratio; ICI = immune checkpoint inhibitor; NA = not available; PFS = progression-free survival; OS = overall survival.

The results of CARMENA and SURTIME demonstrated that patients who require systemic therapy benefit from immediate drug treatment. While randomised trials to investigate deferred vs. no cytoreductive nephrectomy with ICI and ICI combinations are ongoing, the exploratory results from the ICI combination trials demonstrate that the respective Immune-Oncology (IO) + IO or TKI + IO combinations have a superior effect on the primary tumour and metastatic sites when compared to sunitinib alone (Table 7.2). In accordance with the CARMENA and SURTIME data this suggests that mRCC patients and IMDC intermediate- and poor-risk groups with their primary tumour in place should be treated with upfront IO-based combinations. In patients with a clinical response to IO-based combinations, a subsequent CN may be considered. Real-world data have demonstrated durable response and surgical safety with this strategy, however long-term surveillance is lacking [504-506].

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 [309, 462] (see recommendations Section 7.1.2.2.4).

7.3.1.1.2 Summary of evidence and recommendations for local therapy of advanced/metastatic RCC

Summary of evidence	LE
Deferred CN with pre-surgical sunitinib in intermediate-risk patients with clear cell metastatic renal cell carcinoma shows a survival benefit in secondary endpoint analyses and selects out patients with inherent resistance to systemic therapy.	2b
Sunitinib alone is non-inferior compared to immediate CN followed by sunitinib in patients with MSKCC intermediate and poor risk who require systemic therapy with VEGFR-TKI.	1a
Cytoreductive nephrectomy in patients with simultaneous complete resection of a single metastasis or oligometastases may improve survival and delay systemic therapy.	3
Patients with MSKCC or IMDC poor risk do not benefit from CN.	1a
Patients with their primary tumour in place treated with IO-based combination therapy have better PFS and OS in exploratory subgroup analyses compared to treatment with sunitinib.	2b

Recommendations	Strength rating
Do not perform cytoreductive nephrectomy (CN) in MSKCC poor-risk patients.	Strong
Do not perform immediate CN in intermediate-risk patients who have an asymptomatic synchronous primary tumour and require systemic therapy.	Weak
Start systemic therapy without CN in intermediate-risk patients who have an asymptomatic synchronous primary tumour and require systemic therapy.	Weak
Discuss delayed CN with patients who derive clinical benefit from systemic therapy.	Weak
Perform immediate CN in patients with a good performance status who do not require systemic therapy.	Weak
Perform immediate CN in patients with oligometastases when complete local treatment of the metastases can be achieved.	Weak

*7.3.2 **Local therapy of metastases in metastatic RCC***

A SR of the local treatment of metastases from RCC in any organ was undertaken [507]. Interventions included metastasectomy, various radiotherapy modalities, and no local treatment. The outcomes assessed were OS, CSS and PFS, local symptom control and AEs. A risk-of-bias assessment was conducted [508]. Of the 2,235 studies identified only sixteen non-randomised comparative studies were included. Data were too heterogeneous to meta-analyse. There was considerable variation in the type and distribution of systemic therapies (cytokines and VEGF-inhibitors) and in reporting the results. A subsequent SR did not change the quality of evidence [509].

7.3.2.1 Complete versus no/incomplete metastasectomy

A SR, including only eight studies, compared complete vs. no and/or incomplete metastasectomy of RCC metastases in various organs [510-517]. In one study complete resection was achieved in only 45% of the metastasectomy cohort, which was compared with no metastasectomy [517]. Non-surgical modalities were not applied. Six studies [511-513, 515-517] reported a significantly longer median OS or CSS following complete metastasectomy (the median value for OS or CSS was 40.75 months, range 23-122 months) compared with incomplete and/or no metastasectomy (the median value for OS or CSS was 14.8 months, range 8.4-55.5 months). Of the two remaining studies, one [510] showed no significant difference in CSS between complete and no metastasectomy, and one [514] reported a longer median OS for metastasectomy albeit no p-value was provided.

7.3.2.2 Local therapies for RCC bone metastases

Of the three studies identified, one compared single-dose image-guided radiotherapy (IGRT) with hypofractionated IGRT in patients with RCC bone metastases [518]. Single-dose IGRT (> 24 Gy) had a significantly better 3-year actuarial local PFS rate, also shown by Cox regression analysis. Another study compared metastasectomy/curettage and local stabilisation with no surgery of solitary RCC bone metastases in various locations [519]. A significantly higher five-year CSS rate was observed in the intervention group. After adjusting for prior nephrectomy, gender and age, multivariable analysis still favoured metastasectomy/curettage and stabilisation. A third study compared the efficacy and durability of pain relief between single-dose stereotactic body radiotherapy (SBRT) and conventional radiotherapy in patients with RCC bone metastases to the spine [520]. Pain, 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-arm study compared stereotactic radiosurgery (SRS) vs. whole brain radiotherapy (WBRT) vs. SRS and WBRT [521]. 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 intra-cerebral control were equivalent in patients treated with SRS alone and SRS plus 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 and WBRT in a subgroup analysis of RPA class I showed significantly better 2-year OS and intra-cerebral control for SRS plus WBRT based on only three participants. The other study compared fractionated stereotactic radiotherapy (FSRT) with metastasectomy and conventional radiotherapy or conventional radiotherapy alone [522]. Several patients in all groups underwent alternative surgical and non-surgical treatments after initial treatment. One-, two- and three-year survival rates were higher but not significantly so for FSRT as for metastasectomy and conventional radiotherapy, or conventional radiotherapy alone. Fractionated stereotactic radiotherapy did not result in a significantly better two-year local control rate compared with metastasectomy plus conventional radiotherapy.

Stereotactic radiotherapy (SRT) with a median physical dose of 20 (18-30) Gy and a biologically effective dose (DED10) of 63.3 (45-125) Gy in a median (range) of 1 (1-6) fractions for 1-5 brain metastases were safe also during ICI and targeted therapy [479]. Targeted therapy was paused only in one-third of patients for 2-21 days. Local control at all sites, including extracranial, was 75% at one year. After one year, 62% of patients remained on the same systemic therapy as at the time of SRT, which was more frequent for ICI therapy as compared to targeted therapy (83% vs. 36%; p = 0.035). No grade IV or V toxicity was observed.

7.3.2.4 Embolisation of metastases

Embolisation prior to resection of hypervascular bone or spinal metastases can reduce intra-operative blood loss [174]. In selected patients with painful bone or paravertebral metastases, embolisation can relieve symptoms [175] (see recommendation Section 7.1.2.2.4).

7.3.2.5 Stereotactic radiotherapy in oligo-recurrent and oligo-progressive metastases

Sterotatic radiotherapy has been used in oligoprogression (i.e. limited number of metastasis in progression, while other sites are controlled under systemic therapy) and in oligonmetastatic recurrences. Two SRs of single arm studies have been conducted [523, 524]. The non comparative nature of the studies included in both SR does not allow to definate conclusions.

A retrospective analysis of 207 patients with oligo-recurrent and oligo-progressive lesions in mainly bones and lungs with or without systemic therapy (mainly targeted therapy) demonstrated two-year local control rate of 78.3% (95% CI: 72.5-83.0). One, two and three-year local control rates were 89.4%, 80.1% and 76.6% in oligo-recurrent patients, and 82.7%, 76.9% and 64.3% in those with oligo-progressive disease, respectively. Median applied biologically effective dose (BED) 10 was 60 Gy. Median time to subsequent systemic therapy was 13.9 months and median PFS was 37.9 months. No grade III or higher toxicities were reported [525].

Similar results in oligo-progressive mRCC has been reported in a single-arm prospective study including 37 patients with IMDC favourable- and intermediate risk where one-year local control of the irradiated lesions was 93% (95% CI: 71-98%) and median time to change in systemic TKI therapy was 12.6 months (95% CI: 9.6-17.4 months). Median therapy prior to study entry was 18.6 months and therapy was discontinued during SRT. The median BED10 was 72 Gy, corresponding to a SRT dose of 40 Gy in 5 fractions. Median PFS was 9.3 months and there were no reported grade III acute or late toxicities [526]. Several RCTs with SBRT in oligometastatic setting are ongoing.

7.3.2.6 Adjuvant treatment in cM0 patients after metastasectomy

Patients after metastasectomy and no evidence of disease (cM0) have a high risk of relapse. Recent attempts to reduce RFS in randomised prospective phase II trials of sorafonib and pazopanib after metastasectomy did not demonstrate an improvement in RFS [176, 177].

KEYNOTE-564 included a small percentage of patients who were treated by nephrectomy and complete metastasectomy within one year after primary diagnosis (6% in the experimental arm and 6% in the placebo arm) [483, 484]. A metachronous interval of < 1 year for recurrences following surgery with curative intent is a poor prognostic factor by IMDC classification [[267, 527]. Systemic therapy based on immune combinations has stronger levels of evidence than surgery in this intermediate/advanced disease setting [528]. Also, TKI- driven adjuvant trials after metastasectomy have shown no DFS or OS benefit [176, 177].

Results for single-agent pembrolizumab post-surgery for metastatic disease are therefore difficult to interpret due to the small subgroup. Nevertheless, the DFS HR of 0.29 (95% CI: 0.12-0.69) in favour of resection of M1 to NED plus pembrolizumab shows that patients with subclinical, but progressive, disease who were subjected to metastasectomy had a benefit of adjuvant systemic therapy with pembrolizumab. Based on the current data it cannot be concluded that for patients with oligo-progressive disease, metastasectomy within the first year of initial diagnosis of the primary and subsequent adjuvant pembrolizumab is superior to a period of observation and dual IO-based combination first-line therapy upon progression. Data from the TKI era suggest that patients with oligometastatic disease recurrence can be observed for up to a median of sixteen months before systemic therapy is required and that this practice is common in real-world settings (30%) [529, 530].

In addition, it is possible that metastasectomy may lead to poorer outcomes compared to systemic therapy approaches as a relapse within the first twelve months and presentation with synchronous (oligo-metastatic disease is attributed to the IMDC intermediate risk-group. The Panel therefore does not encourage metastasectomy and adjuvant pembrolizumab in this population with recurrent disease within one year after primary surgery. A careful reassessment of disease status to rule out rapid progressive disease should be performed. Data from another adjuvant ICI study with the PD-L1 inhibitor atezolizumab (IMmotion010) also included an M1 NED subgroup which showed no DFS advantage [485]. This result underscores the need for caution in the treatment of the M1 NED subgroup.

7.3.2.7 Summary of evidence and recommendations for local therapy of metastases in metastatic RCC

Summary of evidence	LE
Retrospective comparative studies point towards a benefit of complete metastasectomy in mRCC patients in terms of OS, CSS and delay of systemic therapy.	3
A single-arm prospective and retrospective study support that oligometastases can be observed for up to 16 months before systemic therapy is required due to progression.	2a
Radiotherapy to bone and brain metastases from RCC can induce significant relief from local symptoms (e.g. pain).	3
Tyrosine kinase inhibitors treatment after metastasectomy in patients with no evidence of disease did not improve RFS when compared to placebo or observation.	1b

Recommendations	Strength rating
To control local symptoms, offer ablative therapy, including metastasectomy, to patients with metastatic disease and favourable disease factors and in whom complete resection is achievable.	Weak
Offer stereotactic radiotherapy for clinically relevant bone- or brain metastases for local control and symptom relief.	Weak
Do not offer tyrosine kinase inhibitor treatment to mRCC patients after metastasectomy and no evidence of disease.	Strong
Perform a confirmatory axial scan of disease status prior to metastasectomy to rule out rapid progressive metastatic disease which requires systemic treatment.	Weak
Before initiating systemic therapy for oligometastases that cannot be resected, discuss with your patient a period of observation until progression is confirmed.	Weak

7.4 Systemic therapy for advanced/metastatic RCC

*7.4.1 **Chemotherapy***

Chemotherapy has proven to be generally ineffective in the treatment of RCC but can be offered to patients with collecting duct or medullary carcinoma [178].

7.4.1.1 Recommendation for systemic therapy in advanced/metastatic RCC

Recommendation	Strength rating
Do not offer chemotherapy to patients with metastatic renal cell carcinoma.	Strong

*7.4.2 **Targeted therapies***

In sporadic ccRCC, HIF accumulation due to VHL-inactivation results in overexpression of VEGF and platelet-derived growth factor (PDGF), which promote neo-angiogenesis [531-533]. This process substantially contributes to the development and progression of RCC. Several targeting drugs for the treatment of mRCC are approved in both the USA and Europe.

Most published trials have selected for clear-cell carcinoma subtypes, thus no robust evidencebased 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 IMDC risk model (see chapter 6.6 on prognostic models) [269].

7.4.2.1 Tyrosine kinase inhibitors

7.4.2.1.1 Sunitinib

Sunitinib is an oral TKI inhibitor and has anti-tumour and anti-angiogenic activity. First-line monotherapy with sunitinib demonstrated significantly longer PFS compared with IFN-α. Overall survival was greater in patients treated with sunitinib (26.4 months) vs. IFN-α (21.8 months) despite crossover [534].

In the EFFECT trial, sunitinib 50 mg/day (four weeks on/two weeks off) was compared with continuous uninterrupted sunitinib 37.5 mg/day in patients with clear cell metastatic renal cell carcinoma (cc-mRCC) [535]. 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 time to progression with the standard 50 mg dosage, the authors recommended using this regimen. Alternate scheduling of sunitinib (two weeks on/one week off) is being used to manage toxicity, but robust data to support its use is lacking [536, 537].

7.4.2.1.2 Pazopanib

Pazopanib is an oral angiogenesis inhibitor. In a trial of pazopanib vs. placebo in treatment-naive mRCC patients and cytokine-treated patients, a significant improvement in PFS and tumour response was observed [538].

A non-inferiority trial comparing pazopanib with sunitinib (COMPARZ) established pazopanib as an alternative to sunitinib. It showed that pazopanib was not associated with significantly worse PFS or OS compared to sunitinib. The two drugs had different toxicity profiles, and QoL was better with pazopanib pazopanib [539]. In another patient-preference study (PISCES), patients preferred pazopanib to sunitinib (70% vs. 22%, p < 0.05) due to symptomatic toxicity [540]. Both studies were limited in that intermittent therapy (sunitinib) was compared with continuous therapy (pazopanib).

7.4.2.1.3 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 who had previously failed cytokine treatment or targeted agents (mainly sunitinib) [541].

The overall median PFS was greater for axitinib than sorafenib. Axitinib was associated with a greater PFS than sorafenib (4.8 vs. 3.4 months) after progression on sunitinib. Axitinib showed grade 3 diarrhoea in 11%, hypertension in 16%, and fatigue in 11% of patients. Final analysis of OS showed no significant differences between axitinib or sorafenib [542]. In a randomised phase III trial of axitinib vs. sorafenib in first-line treatment-naive cc-mRCC, a significant difference in median PFS between the treatment groups was not demonstrated, although the study was underpowered, raising the possibility of a type II error [543]. As a result of this study, axitinib is not approved for first-line therapy.

7.4.2.1.4 Cabozantinib

Cabozantinib is an oral inhibitor of tyrosine kinase, 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 [232]. Based on these results an RCT investigated cabozantinib vs. everolimus in patients with ccRCC failing one or more VEGF-targeted therapies (METEOR) [544, 545]. Cabozantinib delayed PFS compared to everolimus in VEGF-targeted therapy refractory disease (HR: 0.58, 95% CI: 0.45-0.75) [544] (LE: 1b). The median OS was 21.4 months (95% CI: 18.7 to not estimable) with cabozantinib and 16.5 months (95% CI: 14.7-18.8) with everolimus in VEGF-resistant RCC. The HR for death was 0.66 (95% CI: 0.53-0.83, p = 0.0003) [500]. Grade III or IV adverse events were reported in 74% with cabozantinib and 65% with everolimus. Adverse events were managed with dose reductions; doses were reduced in 60% of the patients who received cabozantinib.

The Alliance A031203 CABOSUN randomised phase II trial comparing cabozantinib and sunitinib in first-line in 157 intermediate- and poor-risk patients favoured cabozantinib for RR and PFS, but not OS [546, 547]. Cabozantinib significantly increased median PFS (8.2 vs. 5.6 months, adjusted HR: 0.66, 95% CI: 0.46 to 0.95; one-sided p = 0.012). Objective response rate was 46% (95% CI: 34-57) for cabozantinib vs. 18% (95% CI: 10-28) for sunitinib. All-causality grade III or IV adverse events were similar for cabozantinib and sunitinib. No difference

in OS was seen. Due to limitations of the statistical analyses within this trial, the evidence is inferior over existing choices.

7.4.2.1.5 Lenvatinib

Lenvatinib is an oral multi-target TKI of VEGFR1, VEGFR2, and VEGFR3, with inhibitory activity against fibroblast growth factor receptors (FGFR1, FGFR2, FGFR3, and FGFR4), platelet growth factor receptor (PDGFRα), re-arranged during transfection (RET) and receptor for stem cell factor (KIT). It has recently been investigated in a randomised phase II study in combination with everolimus vs. lenvatinib or everolimus alone (see Section 7.4.4.1.1 for discussion of results) [548].

7.4.2.1.6 Tivozanib

Tivozanib is a potent and selective TKI of VEGFR1, VEGFR2, and VEGFR3 and was compared in two phase III trials with sorafenib in patients with mRCC [549, 550]. Tivozanib was approved by the EMA in front-line mRCC. While it was associated with a PFS advantage in both studies, no OS advantage was seen. In view of the choice of sorafenib as the control arm in the front-line trial, the Panel considers there is too much uncertainty, and too many attractive alternatives, to support its use in this front-line setting.

7.4.2.2 Monoclonal VEGF antibody

Bevacizumab is a humanised monoclonal antibody. Initial first-line treatment in combination with IFN-α has been superseded by more effective therapies [551-553]. Bevacizumab in combination with atezolizumab has not been approved for treatment of mRCC (see Section 7.4.3.2) [554].

7.4.2.3 mTOR inhibitors

7.4.2.3.1 Temsirolimus

Temsirolimus is a specific inhibitor of mTOR [555]. Its use has been superseded as front-line treatment option.

7.4.2.3.2 Everolimus

Everolimus is an oral mTOR inhibitor, which is established in the treatment of VEGF-refractory disease. The RECORD-1 study compared everolimus plus best supportive care (BSC) vs. placebo plus BSC in patients with previously failed anti-VEGFR treatment (or previously intolerant of VEGF-targeted therapy) [556]. The data showed a median PFS of 4 vs. 1.9 months for everolimus and placebo, respectively [556].

The Panel consider, even in the absence of conclusive data, that everolimus may present a therapeutic option in patients who were intolerant to, or previously failed, immune- and VEGFR-targeted therapies (LE: 4). Recent phase II data suggest adding lenvatinib is attractive.

7.4.2.4 Small molucule inhibitor.

7.4.2.4.1 Belzutifan

Belzutifan is an inhibitor of the HIF2a transcription factor with single agent activity ccRCC. Initial Phase I/II trials in 55 patients confirmed objective response rate was 25% (all partial responses), and the median progression-free survival was 14.5 months. The most common grade ≥3 adverse events were anemia (27%) and hypoxia (16%) [59]. In the randomised phase III LITESPARK 005, it shows a progression free survival advantage over everolimus in heavily pretreated ccRCC. It has a favorable adverse event profile. It should be considered as an attractive alternative to everolimus in this setting. Overall survival is awaited as are the results of a number of combination studies [557].

7.4.2.5 Vascular endothelial growth factor (VEGF) targeted therapy

Intermittent VEGF targeted therapy is attractive for patients on long term therapy, due to the chronic toxicity associated with long term therapy such as fatigue. It has been tested with sunitinib or pazopainib in a phase III study and found to be safe [558]. Patients in the study had stable disease (or better) for at least six months after staring therapy. They were closely followed for progression with cross sectional imaging. Cessation of therapy was associated with higher rates of progression but no detrimental effect was seen on OS [558]. Intermittent therapy has not been tested with VEFG/PD-1 combinations, therefore its application in the modern 1st line setting is unknown, but extrapolation suggests it should be safe.

7.4.2.6 Summary of evidence and recommendations for single-agent targeted therapy in metastatic clear-cell RCC

Summary of evidence	LE
Single-agent VEGF-targeted therapy has been superseded by immune checkpoint-based combination therapy.	1b
Intermittent VEGF therapy can be considered in patients on long term VEGF targeted therapy	2
IO-VEGFR TKI combination estblished RR and PFS benefot over single agent VEGFR TKI but no OS benefit in subgroup analysis.	1a
Pazopanib is non-inferior to sunitinib as first-line management option in mRCC.	1b
Cabozantinib in intermediate- and poor-risk treatment-naive ccRCC leads to better response rates and PFS but not OS when compared to sunitinib.	2b
Tivozanib has been EMA approved in first-line setting.	3
Single-agent VEGF-targeted therapies are preferentially recommended after first-line PD-L1-based combinations. Re-challenge with treatments already used should be avoided.	3
Single-agent cabozantinib or nivolumab are superior to everolimus after one or more lines of VEGF-targeted therapy.	1b
Everolimus prolongs PFS after VEGF-targeted therapy when compared to placebo. This is no longer widely recommended before third-line therapy.	1b
Belzutifan has a progression free survial advantage over everolimus in second and more lines pretreated clear cell renal cancer.	1b
Lenvatinib in combination with everolimus improved PFS over everolimus alone in VEGF-refractory disease. Its role after ICIs is uncertain. There is a lack of robust data on this combination making its recommendation challenging.	2a

Recommendations	Strength rating
Offer nivolumab or cabozantinib for immune checkpoint inhibitor-naive vascular endothelial growth factor receptor (VEGFR)-refractory clear-cell metastatic renal cell carcinoma (cc-mRCC) after one or two lines of therapy.	Strong
Sequencing the agent not used as second-line therapy (nivolumab or cabozantinib) for third-line therapy is recommended.	Weak
Offer VEGF-tyrosine kinase inhibitors as second-line therapy to patients refractory to nivolumab plus ipilimumab or axitinib plus pembrolizumab or cabozantinib plus nivolumab or lenvatinib plus pembrolizumab.	Weak
Offer cabozantinib after VEGF-targeted therapy in cc-mRCC.	Strong
Sequence systemic therapy in treating mRCC.	Strong
Offer immune checkpoint inhibitor combination therapy for advanced cc-mRCC with sarcomatoid features.	Weak
Offer belzutifan as an alternative to everolimus in patients previously treated with second to fourth line therapy for clear cell renal carcinoma.	Weak
Intermittent single agent VEGFR tyrosine kinase inhibitor can be offered in case of partial response or stable disease > 6 months	Weak

7.4.3 ***Immunotherapy***

7.4.3.1 Immune checkpoint inhibitors

7.4.3.1.1 Immuno-oncology monotherapy

Immune checkpoint inhibitor with monoclonal antibodies targets and blocks the inhibitory T-cell receptor PD-1 or cytotoxic T-lymphocyte-associated antigen 4 (CTLA-4)-signalling to restore tumour-specific T-cell immunity [559]. Immune checkpoint inhibitor monotherapy has been investigated as second- and third-line therapy. A phase III trial of nivolumab vs. everolimus after one or two lines of VEGF-targeted therapy for mRCC with a clear cell component (CheckMate 025, NCT01668784) reported a longer OS, better QoL and fewer grade 3 or 4 AEs with nivolumab than with everolimus [560]. Nivolumab has superior OS to everolimus (HR: 0.73, 95% CI: 0.57-0.93, $p < 0.002$) in VEGF-refractory RCC with a median OS of 25 months for nivolumab and 19.6 months for

everolimus with a 5-year OS probability of 26% vs. 18% [561] (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. Progression-free survival does not appear to be a reliable surrogate of outcome for PD-1 therapy in RCC. Currently PD-L1 biomarkers are not used to select patients for this therapy.

There are no RCTs supporting the use of single-agent ICI in treatment-naive patients. Randomised phase II data for atezolizumab vs. sunitinib showed a HR of 1.19 (95% CI: 0.82-1.71) which did not justify further assessment of atezolizumab as single agent as first-line treatment option in this group of patients, despite high complete response rates in the biomarker-positive population [562]. Single-arm phase II data for pembrolizumab from the KEYNOTE-427 trial show high response rates of 38% (up to 50% in PD-L1+ patients), but a PFS of 8.7 months (95% CI: 6.7-12.2) [562]. Based on these results and in the absence of randomised phase III data, single-agent checkpoint inhibitor therapy is not recommended as an alternative in a first-line therapy setting.

In addition, several trials explored the strategy of nivolumab monotherapy in first-line ccRCC followed by a salvage strategy with nivolumab plus ipilimumab upon progression or if stable disease was the best response. Trial results do not support such a strategy which was frequently not feasible and of limited benefit [563, 564].

7.4.3.2 Immunotherapy/combination therapy

The phase III trial CheckMate 214 (NCT 02231749) showed a superiority of nivolumab and ipilimumab over sunitinib. The primary endpoint population focused on the IMDC intermediate- and poor-risk population where the combination demonstrated an OS benefit (HR: 0.63, 95% CI: 0.44-0.89) which led to regulatory approval [499] and a paradigm shift in the treatment of mRCC [565]. Results from CheckMate 214 further established that the combination of ipilimumab and nivolumab was associated with higher response rates (RR) (39% in the ITT population), complete RR (8% in the ITT population [central radiology review]) and duration of response compared to sunitinib. Progression-free survival did not achieve the pre-defined endpoint. The exploratory analysis of OS data in the PD-L1-positive population was 0.45 (95% CI: 0.29-0.41).

A recent update with 60-month data shows ongoing benefits for the immune combination with independently assessed complete response rates of 11% and a HR for OS in the IMDC intermediate- and poor-risk group of 0.68 (0.58-0.81) [520]. However, this complete response rate has not been consistent across trials for this combination (the Cosmic313 study showed complete response rates of 3% [566]).

In CheckMate 214 the 60-months OS probability was 43% for ipilimumab plus nivolumab vs. 31% for sunitinib, respectively [567]. In this update the IMDC good-risk group did not continue to perform better with sunitinib although this effect occurs due to a late overlap of the Kaplan-Meier curves (HR for OS: 0.94 [95% CI: 0.65-1.37]) [567]. Nivolumab plus ipilimumab was associated with 46% grade III-IV toxicity and 1.5% treatment-related deaths. It should therefore be administered in centres with experience of immune combination therapy and appropriate supportive care within the context of a multidisciplinary team (LE: 4). PD-L1 biomarker is currently not used to select patients for therapy.

The frequency of steroid use has generated controversy and further analysis, as well as real world data, are required. For these reasons the Panel continues to recommend ipilimumab and nivolumab in the intermediate- and poor-risk population.

The KEYNOTE-426 trial (NCT02853331 reported results for the combination of axitinib plus pembrolizumab vs. sunitinib in 861 treatment-naive cc-mRCC patients [568]. Overall survival and PFS assessed by central independent review in the ITT population were the co-primary endpoints. Response rates and assessment in the PD-L1-positive patient population were secondary endpoints. With a minimum follow-up of 35.6 months (median 42.8 months) this trial demonstrated an ongoing OS benefit for axitinib plus pembrolizumab in the ITT population (HR: 0.73, 95% CI: 0.60-0.88, $p < 0.001$). Median OS for axitinib plus pembrolizumab was 45.7 months (95% CI: 43.6 - NR) vs. 40.1 month (95% CI: 34.3 - 44.2) for sunitinib with a PFS benefit (HR: 0.68, 95% CI: 0.58-0.80, $p < 0.0001$) which was shown across all IMDC subgroups for PFS, while OS was similar between axitinib plus pembrolizumab vs. sunitinib in the favourable subgroup with an OS benefit in the IMDC intermediate- and poor-risk groups. The complete response rate by independent review was 10% in the pembrolizumab plus axitinib arm and 4% in the sunitinib arm [569]. With an extended median follow-up of 67 months median OS was 47.2 months (43.6-54.8) vs. 40.8 months (34.3-47.5; HR 0.84 95%CI: 0.71-0.99)) for sunitib, median PFS was 15.7 (13.6-20.2) vs. 11.1 (8.9-12.5) HR 0.69 (95% CI: 0.59-0.81) and ORR was 60.6% (CR 11.6%) vs. 39.6% (CR 4.0%) [570]. Treatment-related adverse events (≥ grade III) occurred in 63% of patients receiving axitinib and pembrolizumab vs. 58% of patients receiving sunitinib. Treatment- related deaths occurred in approximately 1% in both arms [568].

The phase III CheckMate 9ER trial randomised 651 patients to nivolumab plus cabozantinib (n = 323) or vs. sunitinib (n = 328) in treatment-naive cc-mRCC patients [456]. The primary endpoint of PFS assessed by central independent review in the ITT population was significantly prolonged for nivolumab plus cabozantinib (16.6 months) vs. sunitinib (8.3 months, HR: 0.51, 95% CI: 0.41-0.64, p < 0.0001). The nivolumab/cabozantinib combination also demonstrated a significant OS benefit in the secondary endpoint compared with sunitinib (HR: 0.60, CI: 0.40-0.89, p = 0.0010) after a median follow-up of 18.1 months in the initial report [571]. The independently assessed ORR was 55.7% vs. 27.1% with a complete response rate of 8% for nivolumab plus cabozantinib vs. 4.6% with sunitinib. The efficacy was observed independent of IMDC group and PD-L1 status. Treatment-related adverse events (> grade III) occurred in 61% of patients receiving cabozantinib and nivolumab vs. 51% of patients receiving sunitinib. Treatment-related deaths occurred in one patient in the nivolumab/cabozantinib arm and in two patients in the sunitinib arm. With an extended follow-up with median 44 months the median OS was 49.5 months (40.3-not estimable) in the nivolumab plus cabozantinib patients vs. 35.5 months (29.2-42.3) in the sunitinib treated patients (HR: 0.70 [95% CI: 0.56-0.87, p = 0.0043). The updated median PFS was 16.6 months (12.8-19.5) vs. 8.4 months (7.0-9.7; HR 0.59 [95% CI: 0.49-0.71], p < 0·0001 [572].

The randomised phase III trial CLEAR (Lenvatinib/Everolimus or Lenvatinib/Pembrolizumab vs. Sunitinib Alone as Treatment of Advanced RCC) was published [573]. CLEAR randomised a total of 1,069 patients (in a 1:1:1 ratio) to lenvatinib plus pembrolizumab (n = 355) vs. lenvatinib plus everolimus (n = 357) vs. sunitinib (n = 357). The trial reached its primary endpoint of independently assessed PFS at a median of 23.9 vs. 9.2 months, for lenvatinib plus pembrolizumab vs. sunitinib, respectively (HR: 0.39, 95% CI: 0.32-0.49, p < 0.001). Overall survival significantly improved with lenvatinib plus pembrolizumab vs. sunitinib (HR: 0.66, 95% CI: 0.49-0.88, p = 0.005). Objective response for lenvatinib plus pembrolizumab was 71% with 16% of the patients having a complete remission. In the final analyis with a median follow-up of 49.8 months median OS was 53.7 months (48.7-not estimable) for lenvatinib plus pembrolizumab vs. 54.3 (40.9-not estimable; HR 0.79 95% CI: 0.63-0.99) for sunitinib [574]. Efficacy was observed across all IMDC risk groups, independently of PD-L1 status. Treatment-related adverse events (> grade III) with lenvatinib plus pembrolizumab were 72%. Treatment-related death occurred in four patients in the lenvatinib plus pembrolizumab arm and in one patient in the sunitinib arm.

The JAVELIN trial investigated 886 patients in a phase III RCT of avelumab plus axitinib vs. sunitinib [501]. The trial met one of its co-primary endpoints (PFS in the PD-L1-positive population at first interim analysis [median follow up 11.5 months]). Hazard ratios for PFS and OS in the ITT population were 0.69 (95% CI: 0.56-0.84) and 0.78 (95% CI: 0.55-1.08), respectively, but with a missing significant OS improvement also with longer follow-up [575] and in the third interim analyis with a median follow-up of 34.1 months [576]. The same applies to the atezolizumab/bevacizumab combination (IMmotion151) which also achieved a PFS advantage over sunitinib in the PD-L1-positive population at interim analysis and ITT (HR: 0.74, 95% CI: 0.57-0.96), but has not shown a significant OS advantage at final analysis (HR: 0.91 [95% CI: 0.76-1.08], p = 0.27) [554, 577]. Therefore, these combinations cannot currently be recommended.

In IMDC favourable patients the treatment with axitinib+pembrolizumab (Keynote-426), cabozantinib+nivolumab (CheckMate-9ER) and lenvatinib+pembrolizumab (CLEAR) improved PFS and objective response rate, but not OS [570, 572, 574]. Given the long-term follow-up with no OS improvement by the respective TKI+IO combination vs sunitinib, TKI monotherapy becomes a standard of care as an additiional choice in IMDC favourable patients. Although sunitinib was the TKI monotherapy used in theses trials, pazopanib is a valid alternative based on the non-inferiority data of the phase III trial COMPARZ [539].

The COSMIC-313 trial is the first RCT to evaluate a triple combination of cabozantinib (40 mg) plus nivolumab plus ipilimumab vs. nivolumab plus ipilimumab, a current standard of care, in 855 patients with IMDC intermediate- and poor-risk [578]. The primary endpoint of PFS improvement, measured in a PFS ITT of 550 patient was met after 249 events occurred with a HR 0.73 (95% CI: 0.57-0.94, p = 0.013) favouring the triplet therapy. Median PFS was not reached (14.0-NE) vs. 11.3 months (7.7-18.2) in the control arm with a median follow-up of 20.2 months. Overall survival has yet to be reported. Objective response was 43% vs. 36% in the triplet vs. the control arm with a complete response rate of 3% in both arms. Treatment-related adverse events (> grade III) with cabozantinib plus nivolumab plus ipilimumab were 73% vs. 41% in the nivolumab plus ipilimumab control arm. The use of high-dose steroids (> = 40 mg prednisolone or equivalent) was 58% (triplet) vs. 35%. (control). Treatment discontinuation rate of any agent was high in the triplet arm (45%) compared to the doublet (24%), whilst discontinuation of all treatments due to the same adverse events was 12% vs. 5% in the control arm.

Although the primary endpoint of PFS was met, objective response rates of the triplet combination are modest as known for TKI + IO doublets. Treatment-related adverse events are high with a high rate of treatment discontinuation. As the OS rate is currently unknown, the additional benefit of this triplet therapy compared to standard immune-based doublet therapy is still uncertain.

Table 7.4: First line immune checkpoint inhibitor combination trials for clear-cell RCC
Cross trial comparison is not recommended and should occur with caution

Study	N	Experimental arm	Primary endpoint	Risk groups	PFS (mo) Median (95% CI) HR	OS (mo) Median (95% CI) HR
KEYNOTE-426 NCT02853331 Median follow-up 67 months [502, 568-570]	861	PEMBRO 200 mg. IV Q3W plus AXI 5 mg. PO BID vs. SUN 50 mg PO QD 4/2 wk.	PFS and OS in the ITT by BICR	**IMDC** FAV 31% IMD 56% POOR 13% **MSKCC** Not determined	(ITT) PEMBRO + AXI: 15.7 (13.6-20.2) SUN: 11.1 (8.9-12.5) HR: 0.69 (95% CI: 0.59-0.81) p < 0.0001	(ITT) PEMBRO + AXI: 47.2. (43.6-54.8) SUN: 40.8 (34.3-47.5) HR:, 0.84 (95% CI: 0.71[0.99) p = 0.001
JAVELIN 101 NCT02684006 Median follow-up 34.1 months [501, 575, 576]	886	AVE 10 mg/kg IV Q2W plus AXI, 5 mg PO BID vs. SUN 50 mg PO QD 4/2 wk.	PFS in the PD-L1+ population and OS in the ITT by BICR	**IMDC** FAV 22% IMD 62% POOR 16% **MSKCC** FAV 23% IMD 66% POOR 12%	(PD-L1+) AVE + AXI: 13.9 (11.0-17.8) SUN: 8.2 (6.9-9.4) HR: 0.67 (95% CI: 0.57-0.79) p < 0.0001	(PD-L1+) AVE+AXI: NR (40.0-NR) SUN: 36.2 (30.0-NE) HR, 0.81 (95% CI: 0.62-1.04) p = 0.0498
IMmotion151 NCT02420821 Median follow-up 24 months [554, 577]	915	ATEZO 1200 mg fixed dose IV plus BEV 15 mg/kg IV on days 1 and 22 of each 42-day cycle vs. SUN 50 mg PO QD 4/2 wk.	PFS in the PD-L1+ population and OS in the ITT by IR	**IMDC** Not determined **MSKCC** FAV 20% IMD 69% POOR 12%	(PD-L1+) ATEZO + BEV: 11.2 (8.9-15.0) SUN: 7.7 (6.8-9.7) HR: 0.74 (95% CI: 0.57-0.96) p = 0.0217	(ITT) ATEZO + BEV: 36.1 (31.5-42.3) SUN: 35.3 (28.6-42.1NE) HR: 0.91 (95% CI: 0.76-1.08) p = 0.27
CheckMate214 NCT02231749 Median follow-up of 60 months [499, 567]	1096	NIVO 3 mg/kg plus ipilimumab 1 mg/kg IV Q3W for 4 doses then nivolumab 3 mg/kg IV Q2W vs. SUN 50 mg PO QD 4/2 wk.	PFS and OS in the IMDC inter-mediate and poor risk population by BICR	**IMDC** FAV 23% IMD 61% POOR 17% **MSKCC** Not determined	(IMDC IMD/poor) NIVO + IPI: 11.6 (8.4-16.5) SUN: 8.3 (7.0-10.4) HR: 0.73 (95% CI: 0.61-0.87)	(IMDC IMD/poor) NIVO + IPI: 47.0 (35.4-57.4) SUN: 26.6 (22.1-33.5) HR: 0.68 (0.58-0.81) p = < 0.0001

CheckMate9ER **NCT03141177** Median follow-up of 44 months [571, 572, 579]	651	NIVO 240 mg. fixed dose IV every 2 wk. plus CABO 40 mg PO daily vs. SUN 50 mg PO QD 4/2 wk.	PFS in the ITT by BICR	**IMDC** FAV 22% IMD 58% POOR 20% **MSKCC** Not determined	(ITT) NIVO+CABO: 16.6 (12.8-19.5) SUN: 8.4 (7.0-9.7) HR: 0.59 (95% CI: 0.49-0.71) p <0.0001	(ITT) NIVO+CABO: 49.5 (40.3-NE) SUN: 35.5 (29.2-42.3) HR: 0.70 (98.9% CI: 0.56-0.87) p = 0.0034
CLEAR **NCT02811861** Median follow-up of 49.8 months [573, 574, 580]	712	PEMBRO 200 mg IV Q3W plus LEN 20 mg PO QD vs. SUN 50 mg PO QD 4/2 wk.	PFS in the ITT by BIRC	**IMDC** FAV 31% IMD 59% POOR 9% NE 1% **MSKCC** FAV 27% IMD 64% POOR 9%	(ITT) PEMBRO+LEN: 23.9 (20.8-27.7) SUN: 9.2 (6.0-11.0) HR: 0.47 (95% CI: 0.38-0.57) p > 0.001	(ITT) PEMBRO+LEN: 53.7 (48.7-NE) SUN: 54.3 (40.9-NE) HR: 0.79 (95% CI: 0.63-0.99) p = 0.005
COSMIC-313 Median follow-up of 20.2 months [578]	855	NIVO 3 mg/kg plus IPI 1 mg/kg IV Q3W for 4 doses then NIVO 3 mg/kg IV Q2W + CABO 40mg PO QD vs. NIVO 3 mg/kg plus IPI 1 mg/kg IV Q3W for 4 doses then NIVO 3 mg/kg IV Q2W	PFS in the PITT population (first 550 pts. randomised)	**IMDC** IMD 75% POOR 25%	(PITT) NIVO+IPI+CABO: NR (14.0-NE) NIVO+IPI: 11.3 (7.7-18.2) HR: 0.73 (95% CI: 0.57-0.94) p = 0.013	NR

ATEZO = atezolizumab; AVE = avelumab; AXI = axitinib; BEV = bevacizumab; BICR = blinded independent central review; BID = twice a day; CABO = cabozantinib; CI = confidence interval; FAV = favourable; HR = hazard ratio; IPI = ipilimumab; IMD = intermediate; IMDC = Metastatic Renal Cancer Database Consortium; IR = investigator review; ITT = intention-to-treat; IV = intravenous; LEN = lenvatinib; mo = months; MSKCC = Memorial Sloan Kettering Cancer Center; NE = non-estimable; NR = not reached; NIVO = nivolumab; OS = overall survival; PEMBRO = pembrolizumab; PFS = profession-free survival; PITT = PFS intention-to-treat; PO = by mouth; Pts = patients; QD = once a day; Q2W = every 2 weeks; Q3W = every 3 weeks; SUN = sunitinib; wk = weeks.

Patients who stop nivolumab plus ipilimumab because of toxicity require expert guidance and support from a multidisciplinary team before re-challenge can occur (LE: 1). Patients who do not receive the full four doses of ipilimumab due to toxicity should continue on single-agent nivolumab, where safe and feasible (LE: 4).
Treatment past progression with nivolumab plus ipilimumab can be justified but requires close scrutiny and the support of an expert multidisciplinary team [499, 581] (LE: 1).

Patients who stop TKI and IO due to immune-related toxicity can receive single-agent TKI once the adverse events has resolved (LE: 1). Adverse event management, including transaminitis and diarrhoea, require particular attention as both agents may be causative. Expert advice should be sought on re-challenge of ICIs after significant toxicity (LE: 4). Treatment past progression on axitinib plus pembrolizumab or nivolumab plus cabozantinib requires careful consideration as it is biologically distinct from treatment past progression on ipilimumab and nivolumab.

Based on Panel consensus, nivolumab plus ipilimumab, pembrolizumab plus axitinib and nivolumab plus cabozantinib and lenvatinib plus pembrolizumab should be administered in centres with experience of immune combination therapy and appropriate supportive care within the context of a multidisciplinary team (LE: 4).

*7.4.4 **Therapeutic strategies***

7.4.4.1 Treatment-naïve patients with clear-cell metastatic RCC

The combination of pembrolizumab plus axitinib as well as nivolumab plus cabozantinib and lenvatinib plus pembrolizumab is the standard of care in all IMDC-risk patients and ipilimumab plus nivolumab in IMDC intermediate- and poor-risk patients (Figure 7.1). Therefore, the role of VEGFR-TKIs alone in front-line mRCC has been superseded in IMDC intermidiate and poor risk. In IMDC Favorable group, in the absence of OS benefit both options are acceptable. Sunitinib, pazopanib, and cabozantinib (IMDC intermediate- and poor-risk disease), remain alternative treatment options for patients who cannot receive or tolerate immune checkpoint inhibition in this setting (Figure 7.1).

7.4.4.1.1 Sequencing systemic therapy in clear-cell metastatic RCC

The sequencing of targeted therapies is established in mRCC and maximises outcomes [548, 560]. Pembrolizumab plus axitinib, nivolumab plus cabozantinib, lenvatinib plus pembrolizumab and nivolumab plus ipilimumab are the new standard of care in front-line therapy in IMDC intermediate/poor. The impact of front-line immune checkpoint inhibition on subsequent therapies is unclear. Randomised data on patients with disease refractory to either nivolumab plus ipilimumab or TKI plus IO in a first-line setting are limited. Sequencing immune checkpoint inhibition with atezolizumab did not demonstrate ORR, PFS , OS benefit over single agent TKI in the CONTACT 03 [582, 583]. Prospective data on cabozantinib, tivozanib, and axitinib are available for patients progressing on immunotherapy, but these studies do not focus solely on the front-line setting, involve subset analyses, and are too small for definitive conclusions [560, 584].

The use of mTOR inhibitors can be considered in VEGF-targeted therapy refractory disease but has been outperformed by other VEGF-targeted therapies in mRCC and belzutifan [585]. Drug choice in the third-line setting, after immune checkpoint inhibitor combinations and subsequent VEGF-targeted therapy, is unknown. The Panel recommends a subsequent agent which is approved in VEGF-refractory disease, with the exception of re-challenge with immune checkpoint blockade. Cabozantinib is the only agent in VEGF-refractory disease with RCT data showing a survival advantage and should be used preferentially [518]. Axitinib has positive PFS data in VEGF- refractory disease. Both sorafenib and everolimus have been outperformed by other agents in VEGF-refractory disease and are therefore less attractive [585]. The lenvatinib plus everolimus combination appears superior to everolimus alone and has been granted EMA regulatory approval based on randomised phase II data. This is an alternative despite the availability of phase II data only [548]. As shown in a study which also included patients on ICIs, tivozanib provides PFS superiority over sorafenib in VEGF-refractory disease [586].

7.4.4.1.2 Summary of evidence and recommendations for immunotherapy in cc-mRCC

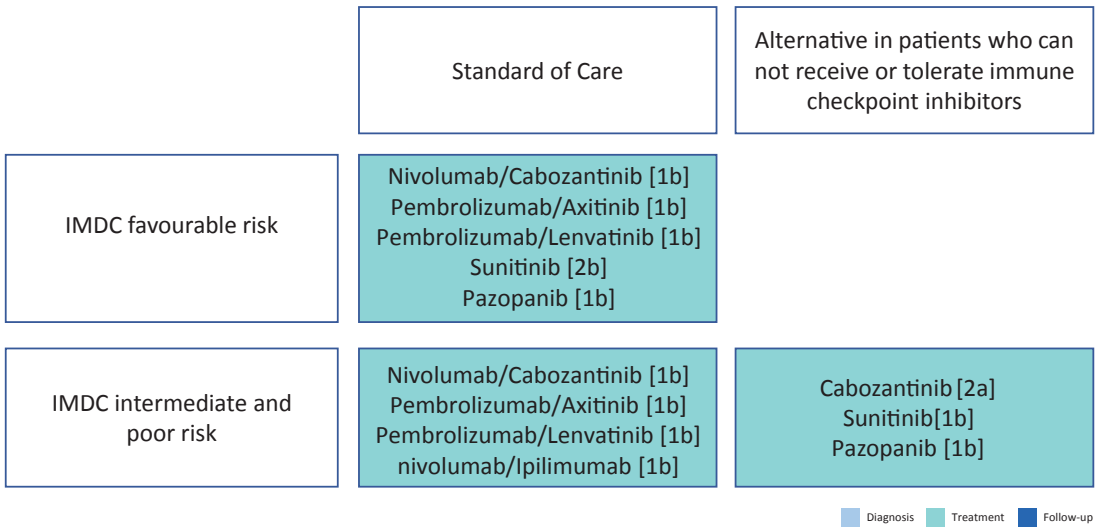
Summary of evidence	**LE**
Treatment-naïve patients	
Currently, PD-L1 expression is not used for patient selection.	2b
The combination of nivolumab and ipilimumab in treatment-naïve patients with cc-mRCC of IMDC intermediate- and poor risk demonstrated OS and ORR benefits compared to sunitinib alone.	1b
The combination of pembrolizumab plus axitinib, lenvatinib plus pembrolizumab and nivolumab plus cabozantinib in treatment-naïve patients with cc-mRCC demonstrated PFS, OS and ORR benefits compared to sunitinib in the ITT population.	1b
The combination of pembrolizumab plus axitinib, lenvatinib plus pembrolizumab and nivolumab plus cabozantinib in treatment-naïve patients with cc-mRCC in IMDC favorable subgroups demonstrated PFS and ORR benefits compared to sunitinib, without OS improvememt.	2b
Triplet CABO-NIVO-IPI demonsrated a PFS benefit over NIVO-IPI.	1b
Nivolumab plus ipilimumab, pembrolizumab plus axitinib, nivolumab plus cabozantinib and lenvatinib plus pembrolizumab should be administered in centres with experience of immune combination therapy and appropriate supportive care within the context of a multidisciplinary team.	4
Sequencing systemic therapy	
Nivolumab leads to superior OS compared to everolimus in disease progression after one or two lines of VEGF-targeted therapy.	1b
Axitinib, cabozantinib or lenvatinib can be continued if immune-related adverse events result in cessation of axitinib plus pembrolizumab, cabozantinib plus nivolumab or lenvatinib plus pembrolizumab. Re-challenge with immunotherapy requires expert support.	4

Patients who do not receive the full four doses of ipilimumab due to toxicity should continue on single-agent nivolumab, where safe and feasible. Re-challenge with combination therapy requires expert support.	4
Treatment past progression can be justified but requires close scrutiny and the support of an expert multidisciplinary team.	1b
Nivolumab plus ipilimumab was associated with 46% grade III-IV toxicity and 1.5% treatment-related deaths. Tyrosine kinase inhibitor-based IO combination therapies were associated with grade III-V toxicity ranging between 61-72% and 1% of treatment-related deaths.	1b
In the CONTACT 3 study atezolizomab plus cabozantinib offer no benefit compared to cabozantinib alone in patients who's cancers have previously progressed on immune checkpoint inhibition therapy.	1b
Cabozantinib as a single agent has the most robust data after first line PD1 based combination therapy.	3

Recommendations	**Strength rating**
First line Treatment for metastatic clear cell RCC patients	
Offer treatment with PD1 combinations in centres with experience.	Weak
Offer nivolumab plus ipilimumab, pembrolizumab plus axitinib, lenvatinib plus pembrolizumab or nivolumab and cabozantinib to patients with International Metastatic Renal Cell Carcinoma Database Consortium (IMDC) intermediate- or poor risk-disease.	Strong
Offer pembrolizumab plus axitinib, lenvatinib plus pembrolizumab or nivolumab and cabozantinib or sunitinib or pazopanib for IMDC favourable risk disease.	Weak
Offer sunitinib or pazopanib to patients with any IMDC risk who cannot receive or tolerate immune checkpoint inhibition.	Strong
Offer cabozantinib to patients with IMDC intermediate- and poor-risk clear cell metastatic renal carcinoma (cc-mRCC) who cannot receive or tolerate immune checkpoint inhibition.	Strong[a]
Patients who do not receive the full four doses of ipilimumab due to toxicity should continue on single-agent nivolumab, where safe and feasible. Re-challenge with combination therapy requires expert support after discontinuation for toxicity.	Weak
Sequencing systemic therapy for metastatic clear cell RCC	
Sequence systemic therapy in treating mRCC.	Strong
Offer carbozantinib or other vascular endothelial growth factor (VEGF)-tyrosine kinase inhibitors as second-line therapy to patients refractory to nivolumab plus ipilimumab or axitinib plus pembrolizumab or cabozantinib plus nivolumab or lenvatinib plus pembrolizumab.	Weak
Sequencing the agent not used as second-line therapy (nivolumab or cabozantinib) for third-line therapy is recommended.	Weak
Offer nivolumab or cabozantinib for those patients who received first line VEGF targeted therapy alone.	Strong
Treatment past progression can be justified but requires close scrutiny and the support of an expert multi-disciplinary team.	Weak
Do not re-challenge patients who stopped immune checkpoint inhibitors because of toxicity without expert guidance and support from a multi-disciplinary team.	Strong
Do not offer PD-L1 combination therapy after progression after immune checkpoint inhibition combination.	Weak

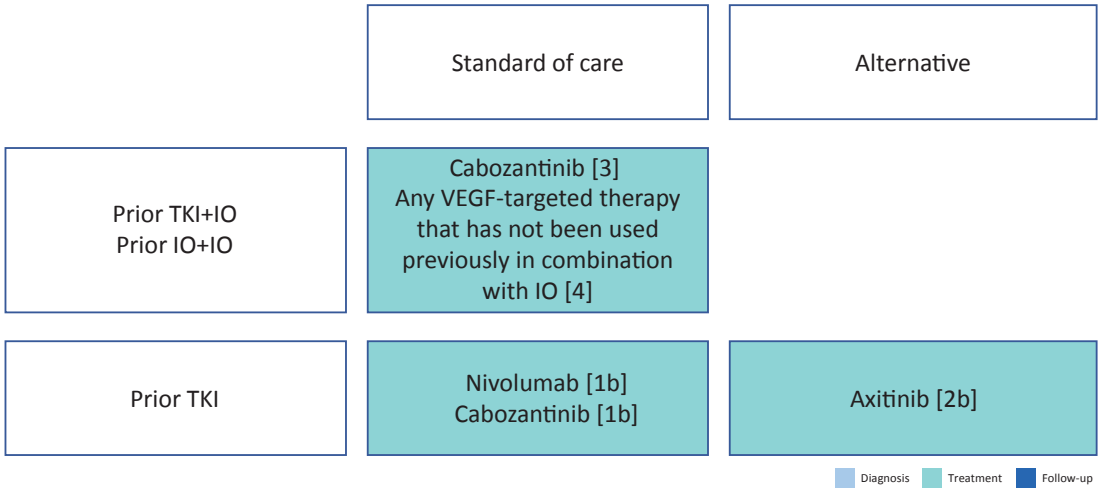
[a] *WWhile this is based on a randomised phase II trial, cabozantinib (weak) looks at least as good as sunitinib in this population. This justified the same recommendation under exceptional circumstances.*

Figure 7.1: Updated EAU Guidelines recommendations for the first-line treatment of cc-mRCC



IMDC = The International Metastatic Renal Cell Carcinoma Database Consortium.
**pazopanib for intermediate-risk disease only.*
[1b] = based on one randomised controlled phase III trial.
[2a] = based on a well-designed study without randomisation, or a subgroup analysis of a randomised controlled trial.

Figure 7.2: EAU Guidelines recommendations for later-line therapy



IO = immunotherapy; TKI = tyrosine kinase inhibitors; VEGF = vascular endothelial growth factor.
[1b] = based on one randomised controlled phase III trial.
[2b] = subgroup analysis of a randomised controlled phase III trial.
[4] = expert opinion.

7.4.4.1.3 Renal tumours with sarcomatoid features

Subset analyses have shown improved results for PD-L1 inhibitors combined with CTLA4 or VEGF-targeted therapy in renal tumours with sarcomatoid features. Ipilimumab/nivolumab, axitinib/pembrolizumab and lenvatinib/pembrolizumab avelumab/axitinib can all be recommended instead of VEFG-targeted therapy alone. These options have OS advantages over sunitinib and superseded VEGF-targeted therapy. Nivolumab/Ipilimumab provided *post hoc* analysis demonstrating ORR of 61%, including 23% CR rate, PFS and OS benefit over sunitinb (HR 0.50 and OS HR 0.46 respectively with median OS 48.6 vs 14.2 month [587].

Table 7.5: Subgroup analysis of first-line immune checkpoint inhibitor combinations in RCC patients with sarcomatoid histology
Cross trial comparison is not recommended and should occur with caution

Study	N (ITT)	Therapy	N (sRCC)	PFS (mo.) Median (95% CI) HR	OS (mo.) Median (95% CI) HR	ORR (%) (95% CI)
KEYNOTE-426 NCT02853331 Median follow-up 12.8 months [568]	861	PEMBRO + AXI SUN	51 54	NR 8.4 HR: 0.54 (0.29-1.00)	NR NR HR: 0.58 (0.21–1.59)	58.8 31.5
JAVELIN 101 NCT02684006 [588, 589]	886	AVE + AXI SUN	47 61	7.0 (5.3-13.8) 4.0 (2.7-5.7) HR 0.57 (0.33-1.00)	NA	46.8 (32.1-61.9) 21.3 (11.9-33.7)
IMmotion151 NCT02420821 Median follow-up 13 to 17 months [590]	915	ATEZO + BEV SUN	68 74	8.3 (5.4, 12.9) 5.3 (3.3, 6.7) HR: 0.52 (0.34-0.79)	21.7 (15.3, NE) 15.4 (10.4, 19.5) HR: 0.64 (0.41, 1.01)	49 (36-1) 14 (7-23)
CheckMate214 NCT02231749 minimum follow-up of 60 months [587]	1096	NIVO + IPI SUN	IMDC Intermediate and poor risk 74 75	26.5 (7.2-NE) 5.5 (4.1-6.9) HR: 0.50 (0.32–0.80)	48.6 (25.2–NE) 14.2 (9.3–22.9) HR: 0.46 (0.29–0.71)	60.8 (48.8-72.0) 23.1 (13.5-35.2)
CheckMate 9ER NCT03141177 Median follow-up 16 months [591]	651	NIVO + CABO SUN	34 41	10.3 (5.6-19.4) 4.2 (2.6-8.3) HR: 0.42 (0.23-0.74)	NR (22.8-NE) 19.7 (8.9-29.5) HR: 0.36 (0.17-0.79)	55.9 (37.9-72.8) 22.0 (10.6-37.6)
CLEAR NCT02811861 Median follow-up 27 months [573, 592]	712	PEMBRO + LEN SUN	28 21	11.1 5.5 HR: 0.39 (0.18-0.84)	NE NE HR: 0.91 (0.32-2.58)	60.7 23.8

ATEZO = atezolizumab; AVE = avelumab; AXI = axitinib; BEV = bevacizumab; CABO = cabozantinib; CI = confidence interval; HR = hazard ratio; IPI = ipilimumab; ITT = intention-to-treat; mo = months; NA = not available; NE = non-estimable; NR = not reached; NIVO = nivolumab; OS = overall survival; PEMBRO = pembrolizumab; PFS = profession-free survival; sRCC = sarcomatoid RCC; SUN = sunitinib.

7.4.4.1.3.1 Summary of evidence and recommendation for targeted therapy in RCC with sarcomatoid features

Summary of evidence	LE
Immune checkpoint inhibitor combination therapy is superior to sunitinib in terms of PFS and OS in trial subset analysis of clear-cell RCC with sarcomatoid features.	2a

Recommendation	Strength rating
Offer immune checkpoint inhibitor combination therapy for advanced clear cell metastatic renal carcinoma with sarcomatoid features.	Weak

7.4.4.2 Treatment of patients with non-clear-cell metastatic RCC (general considerations)

For the sake of historical purposes, the Panel recognises the use of Non-cc-mRCC but will where possible refer to the distinct subtype. This is a heterogenous group including papillary, chromophobe and other rare tumours with a widely differing tumour biology. Patients with non-cc-mRCC should therefore be referred to a clinical trial, where appropriate.While no phase III trials of patients with non-cc-mRCC have been reported it is increasingly recognised to study specific subtypes which have a higher incidence than other non-ccRCC. As papillary RCC (pRCC) comprise the majority of tumours defined as non-ccRCC, most of the evidence is available for this subtype, either from trials specifically selecting pRCC or having included a high percentage.

7.4.4.2.1 Treatment of patients with papillary metastatic RCC

There are small single-arm trials for sunitinib and everolimus [593-597]. Both these agents have been widely given in pRCC, but more recent data suggests cabozantinib and other combinations may be preferable [598, 599].

For pRCC new evidence is available from the SWOG PAPMET randomised phase II trial which compared sunitinib to cabozantinib, crizotinib and savolitinib in 152 patients with papillary mRCC [598]. Progression- free survival was longer in patients in the cabozantinib group (median 9.0 months, 95% CI: 6-12) than in the sunitinib group (5.6 months, CI: 3-7; HR for progression or death 0.60 [0.37-0.97, one-sided p = 0.019]). Response rate for cabozantinib was 23% vs. 4% for sunitinib (two-sided p = 0.010). Savolitinib and crizotinib did not improve PFS compared with sunitinib. Grade III or IV adverse events occurred in 69% (31/45) of patients receiving sunitinib, 74% (32/43) of patients receiving cabozantinib, 37% (10/27) receiving crizotinib, and 39% (11/28) receiving savolitinib; one grade V thromboembolic event was recorded in the cabozantinib group. These results support adding cabozantinib as an option for patients with papillary mRCC based on superior PFS results compared to sunitinib.

In addition, savolitinib was investigated in the SAVOIR trial [599] as first-line treatment for MET-driven tumours defined as chromosome 7 gain, MET amplification, MET kinase domain variations or hepatocyte growth factor amplification by DNA alteration analysis (~30% of screened patients were MET positive). In a limited patient group, savolitinib (n = 27) was compared with sunitinib (n = 33). The trial was stopped early, largely due to poor accrual. The efficacy data appeared to favour savolitinib (median PFS 7.0 months, 95% CI: 2.8 months-NR vs. 5.6 months, 95% CI: 4.1-6.9 months, PFS HR: 0.71, 95% CI: 0.37-1.36, OS HR: 0.51,94% CI: 0.21-1.17, RR: 27% vs. 7%, for savolitinib and sunitinib, respectively). The median OS for savolitinib was not reported, Savolitinib was better tolerated compared with sunitinib with 42% grade > 3 AEs compared to 81% with sunitinib. There are ongoing trials to confirm these findings. The results on these trials are required before recommendations can be made.

Evidence for TKI + IO based combination is derived from two phase II studies of lenvatinib plus pembrolizumab and cabozantinib and nivolumab. The Keynote-B61 phase II trial investigated lenvatinib plus pembrolizumab administered to non-ccRCC patients of whom 93 patients (59%) with pRCC [600, 601]. The primary endpoint of objective response was 54% in pRCC patients, with a median follow-up of 14.9 months, providing some evidence of good efficacy for TKI + IO based combinations. The cabozantinib and nivolumab study enrolled 40 patients with papillary and unclassified RCC with a response rate of 47% and a PFS of 13 (7-16) months [602]. In this trial chromophobe RCC was excluded and the percentage of pRCC was 68%. Indirect comparisons suggest these data compare to an increased efficacy with those of VEGFR-TKI monotherapy alone.
Efficacy for pembrolizumab in the pRCC subset (118/165) was; RR: 29%, PFS: 5.5 months (95% CI: 3.9-6.1 months) and OS: 31.5 months (95% CI: 25.5 months-NR), but these results are based on a single-arm phase II study [603]. Pembrolizumab can be considered in this setting due to the high unmet need; although the VEGFR TKI + IO combination may be preferable.

7.4.4.2.2 Summary of evidence and recommendations for systemic therapy in papillary metastatic RCC

Summary of evidence	LE
Cabozantinib improved PFS over sunitinib in patients with advanced pRCC without additional molecular testing.	2a
Lenvatinib plus pembrolizumab and cabozantinib plus nivolumab demonstrated response rates of 47-54% with median PFS rates >12 months	2a
Pembrolizumab resulted in long-term median OS in a single-arm study in the pRCC subgroup.	2a

Recommendations	Strength rating
Offer cabozantinib to patients with papillary RCC (pRCC) based on a positive randomised controlled trial.	Weak
Offer lenvatinib plus pembrolizumab or nivolumab plus cabozantinib to patients with pRCC based on small single-arm trials.	Weak

7.4.4.2.3 Treatment of patients with metastatic non-ccRCC other than papillary RCC

The evidence surrounding systemic therapy for non-ccRCC tumours other than pRCC is especially weak and has relied on subset analysis of randomised phase II trials as well as expanded access programmes. Results consistently demonstrate that the outcome of these patients with targeted therapy is poorer than for ccRCC. Treatment in non-cc-mRCC has focused on temsirolimus, everolimus, sorafenib, sunitinib, cabozantinib and pembrolizumab in the past [593, 602, 604-606]. Recent data of single-arm phase II trials of lenvatinib plus pembrolizumab demonstrated clinical efficacy of this IO+TKI combinations in different non-ccRCC subgroups. [600, 601, 607]. Meadian ORR across the different non-ccRCC subgroups of 158 patiens was 49%, 12 months PFS and OS rates were 63% and 82%.

7.4.4.2.4 Summary of evidence and recommendation for systemic therapy in chromophobe and unclassified RCC

Summary of evidence	LE
Both mTOR inhibitors and VEGF-targeted therapies have limited activity in non-cc-mRCC. There is a non-significant trend for improved oncological outcomes for sunitinib over everolimus and for cabozantinib over sunitinib.	2a
In non-cc-mRCC, sunitinib improved PFS over everolimus in a SR of phase II trials and subgroups of patients.	1a
In non—cc-mRCC lenvatinib plus pemrolizumab demonstrated clinical efficacy in different non-ccRCC subgroups	2a
In non—cc-mRCC cabozantinib plus nivolumab demonstrated clinical efficacy in different non-ccRCC subgroups except for chromophobe RCC which were excluded from the study	2a

Recommendations	Strength rating
Offer sunitinib to patients with other non-clear cell renal cell carcinoma (cc-RCC) subtypes than papillary RCC.	Weak
Offer lenvatinib plus pembrolizumab to patients with non-ccRCC subtypes.	Weak
Offer cabozantinib and nivolumab to patients with non-ccRCC subtypes other than chromophobe RCC.	weak

7.4.4.3 Renal medullary carcinoma

SMARCB1-deficient renal medullary carcinoma is one of the most aggressive RCCs [68, 199] and most patients (~67%) will present with metastatic disease [29, 68]. Even patients who present with seemingly localised disease may develop macro metastases shortly thereafter, often within a few weeks.

Despite treatment, median OS is thirteen months in the most recent series [33]. Due to the infiltrative nature and medullary epicentre of RMC, RN is favoured over PN even in very early-stage disease. Retrospective data indicate that nephrectomy in localised disease results in superior OS (16.4 vs. 7 months) compared with systemic chemotherapy alone, but longer survival was noted in patients who achieved an objective response to first-line chemotherapy [33, 608]. There is currently no established role for distant metastasectomy or nephrectomy in the presence of metastases.

Palliative radiation therapy is an option and may achieve regression in the targeted areas, but it will not prevent progression outside the radiation field [609, 610]. Renal medullary carcinoma is refractory to monotherapies with targeted anti-angiogenic regimens including TKIs and mTOR inhibitors [33, 173]. The mainstay systemic treatments for RMC are cytotoxic combination regimens which produce partial or complete responses in ~29% of patients [173]. There are no prospective comparisons between different chemotherapy regimens, but most published series used various combinations of platinum agents, taxanes, gemcitabine, and/or anthracyclines [33, 34]. High-dose-intensity combination of MVAC has also shown efficacy against RMC [611] although a retrospective comparison did not show superiority of MVAC over cisplatin, paclitaxel, and gemcitabine [34]. Single-agent anti-PD-1 immune checkpoint therapy has produced responses in a few case reports, although, as yet insufficient data are available to determine the response rate to this approach [609, 610]. Whenever possible, patients should be enrolled in clinical trials of novel therapeutic approaches, particularly after failing first-line cytotoxic chemotherapy.

7.4.4.3.1 Other rare tumours

Knowledge about the systemic treatment of rare tumors is very limited, mostly based on a set of case reports. For some facts about therapy of renal tumours see chapter 3.5 and table 3.2.

Metastatic collecting duct carcinoma (CDC) has a lowest mortality in concomitant use of cytoreductive nephrectomy and systemic therapy [612]. Systemic therapy was investigated in BONSAI phase II trial. Nivolumab showed cilical benefit in 60 % as a second-line therapy after cabozantinib failure [613].

TFE3-rearranged RCC showed objective response rate 25 % with ICI and 0 % with TKI and more prolonged OS (62.4 months with ICI vs 10.3 with TKI). Cabozantinib may be an exeption with 16.6% objective response. There is discussed future role of ICI-TKI combination (such as nivolumab plus cabozantinib) and cabozantinib plus belzutifan [614].

TFEB-altered RCC:

TFEB-rearranged RCC: There is a general lack of information regarding the response to moderm systemic therapy. Combination of ICI and mTOR inhibitors are discussed. *TFEB*-amplified RCC (it occurs in elderly patients and displays more aggressive behaviour compared to *TFEB*-rearranged RCC) can be treated with VEGFR targeting agents or with VEGFR-TKI combination [614].

Some studies combine therapy *TFE3*- and *TFEB*-altered RCCs (because of former grouping ob both tumours to MiT family translocation RCCs). One retrospective study exhibit efficacy of ICI or ICI-TKI combination [615]. Other study provided evidence of the activity of cabozantinib in MiT TRCC, with more durable responses than those observed historically with other VEGFR-TKIs or ICIs [616].

In fumarate hydratase-deficient RCC with high metastatic potential, ICI monotherapies offer a better disease control rate than TKI monotherapies. In phase II trial, ORR of 51 % of combination of erlotinib and bevacizumab [614]. Other trial expressed a favorable response to ICI/TKI combinational therapy comparred to bevacizumab plus erlotinib [92].

Succinate dehydrogenase (SDH)-deficient RCC has a low risk of metastasis (12 %) with exception of high-grade with risk 70 %. Due to rarity of disease, no evidence for systemic therapy [614].

Anaplastic lymphoma kinase (ALK)-rearranged RCC, there are some reports of the efficacy of ALK inhibitors, e.g. entrectinib [614]. ELOC (formerly TCEB1)-mutated RCC doesn't exhibit cinically aggressive behaviour [614].

There is no data that indicates a recommendation for one treatment over another.

7.4.4.4 Treatment of hereditary RCC

7.4.4.4.1 von-Hippel-Lindau-disease-associated RCC

Patients with VHL disease often develop RCC and tumours and cysts in other organs including adrenal glands, CNS, retinal haemangioblastomas, and pancreas, and commonly undergo several surgical resections in their lifetime. In VHL disease, belzutifan, a HIF-2α inhibitor, has been approved by the US Food and Drug Administration (FDA, August 2021) for the treatment of ccRCC and other neoplasms associated with VHL for

the treatment of tumours that do not require immediate surgery. Approval was based on the results from a phase II, open-label, single-arm trial in 61 patients with tumours not larger than 3 cm [59]. Belzutifan induced partial responses with an RCC ORR of 49%, and a disease control rate of 98.4% after 21.8 months treatment. All patients with pancreatic lesions had an ORR of 77%, and those with CNS haemangioblastoma had a 30% response rate. In total, 33% of patients reported > grade III adverse events, and seven patients (11.5%) discontinued the treatment. In the treatment with pazopanib for VHL only 52% continued with the treatment after 24 weeks [617]. A longer follow-up at 37.8 months, ORR for RCC was increased to 64%, with a median time to response of 11.1 months (range, 2.7 to 30.5). Median duration of response per Kaplan-Meier estimate was not reached (range, 5.4+ to 35.8+ months). Thirty-four of 39 patients with a confirmed response (87%) remain in response as of the data cut-off date (September 2022) [557].

With favourable efficacy results and with relatively low-grade side effects, belzutifan seems to be a valuable contribution to the treatment of patients with the VHL disease. The EMA has not yet considered belzutifan for approval in VHL disease.

7.5 Locally-recurrent RCC after treatment of localised disease

Most studies reporting on local recurrent disease after removal of the kidney have not considered the true definition of local recurrence after RN, PN and thermal ablation, which are: local recurrence in the tumour-bearing kidney, tumour growth exclusively confined to the true renal fossa, recurrences within the renal vein, the ipsilateral adrenal gland or the regional LNs. In the existing literature the topic is weakly investigated and often regarded as local recurrent disease.

RECUR is a protocol-based multicentre European registry capturing patient and tumour characteristics, risk of recurrence (RoR), recurrence patterns, and survival of those curatively treated for nonmetastatic RCC from 2006 to 2011. Per-protocol resectable disease (RD) recurrence was defined as (1) solitary metastases, (2) oligometastases, or (3) renal fossa or renal recurrence after radical or partial nephrectomy, respectively. Within the RECUR consortium, the authors assessed the effectiveness of local treatment of resectable recurrent RCC after surgical treatment of the primary kidney tumour [618]. Of 3039 patients with localised RCC treated with curative intent, 505 presented with recurrence, including 176 with RD. Of these patients, 97 underwent local treatment of recurrence (LTR) and 79 no LTR. The median OS was 70.3 mo versus 27.4 in the LTR versus no-LTR group ($p < 0.001$). The LTR effect on survival was consistent across risk groups. OS HR for high, intermediate, and low risks were 0.36 (0.2-0.64), 0.27 (0.11-0.65), and 0.26 (0.08-0.8), respectively. Local treatment of recurrence was associated with longer survival across groups with a risk of recurrence [618]

7.5.1 Locally-recurrent RCC after nephron-sparing approaches

Locally-recurrent disease can affect the tumour-bearing kidney after PN or focal ablative therapy such as RFA and cryotherapy. Local relapse may be due to the incomplete resection of the primary tumour, in a minority of the cases to the local spread of the tumour by microvascular embolisation, or true multifocality [214, 619].

The prognosis of recurrent disease not due to multifocality is poor, despite salvage nephrectomy [619]. Recurrent tumour growth in the regional LNs or ipsilateral adrenal gland may reflect metachronous metastatic spread (see Section 7.3). After treatment solely for localised disease, systemic progression is common [620, 621].

There are reports that minimally invasive approaches (laparoscopic and robotic) show atypical reoccurence (e.g. peritoneal, port site, etc) [622, 623]. Therefore, specific maneuvers to prevent tumour-cell contamination should be implemented. Those include the use of extraction bags, minimising trocar CO2 leakage, avoiding tumour morcellation, cleansing of instruments before reuse, changing of gloves after tumour extraction, avoiding violation of the tumor's natural capsule, and cleansing of port sites [622, 623].

A retrospective study relying on inverse probability of treatment weighting (IPTW) and comparing percutaneous ablation (PCA) and surgical resection (SR) for an isolated local recurrence (LR) following PN [624]. A total of 81 patients with an isolated LR were included. Percutaneous ablation was associated with a lower risk of post-operative complications (odds ratio=0.22; $p = 0.006$) and a smaller change in eGFR. There were no significant differences in the risk of disease, new LR (HR = 1.51; $p = 0.59$), and distant metastasis (HR = 0.19; $p = 0.09$) [624].

Following thermal ablation or cryotherapy generally intra-renal, but also peri-renal, recurrences have been reported in up to 14% of cases [625]. Whereas repeat ablation is still recommended as the preferred therapeutic option after treatment failure, the most effective salvage procedure as an alternative to complete nephrectomy has not yet been defined.

*7.5.2 **Locally-recurrent RCC after radical nephrectomy***

Isolated local fossa recurrence is rare and occurs in about 1-3% after radical nephrectomy. More commonly in pT3-4 than pT1-2 and grade III-IV disease. Most patients with local recurrence of RCC are diagnosed by either CT/MRI scans as part of the post-operative follow-up [626]. The median time to recurrence after RN was 19-36 months in isolated local recurrence or 14.5 months in the group including metastatic cases as well [626-628].

Isolated local recurrence is associated with worse survival [214, 629]. Based on retrospective and non-comparative data only, several approaches such as surgical excision, radiotherapy, systemic treatment and observation have been suggested for the treatment of isolated local recurrence [630-632]. Among these alternatives, surgical resection with negative margins remains the only therapeutic option shown to be associated with improved survival [629]. Open surgery has been successfully reported in studies [633, 634]. One of the largest series including 2,945 patients treated with RN reported on 54 patients with recurrent disease localised in the renal fossa, the ipsilateral adrenal gland or the regional LNs as sole metastatic sites [630]. Another series identified 33 patients with isolated local recurrences and 30 local recurrences with synchronous metastases within a cohort of 2,502 surgically treated patients, confirming the efficacy of locally directed treatment vs. conservative approaches (observation, systemic therapy) [635]

The 5-year OS with isolated local recurrence was 60% (95% CI: 0.44-0.73) and 10-year OS was 32% (95% CI: 0.15-0.51). Overall survival differed significantly by the time period between primary surgery and occurrence of recurrence (< 2 years vs. > 2 years: 10-year OS rate 31% (95% CI: 10.2-55.0) vs. 45% (95% CI: 21.5-65.8; HR: 0.26; p = 0.0034) [626]. Metastatic progression was observed in 60 patients (58.8%) after surgery [627]. Patient survival can be linked to the type of treatment received, as shown in a cohort of 96 patients, 45.8% were metastatic at the time of recurrence; three-year CSS rates after local recurrence were 92.3% ± 7.4%) for those who were treated with surgery and systemic therapy, 63.2% ± 13.2%) for those who only underwent surgery, 22.7% ± 0.9%) for those who only received systemic therapy and 20.5% ± 10.4%) for those who received no treatment (p < 0.001) [628]. A retrospective multi-centre study of patients with Local Retroperitoneal Recurrence (RPR) after radical nephrectomy (RN) with or without surgical treatment from 2008 to 2020. Retroperitoneal Recurrence of RCC was defined as an ipsilateral recurrence confined to the renal fossa, adrenal gland or retroperitoneal lymph nodes after prior nephrectomy, which was diagnosed by cross-sectional imaging. Treatment with RPR surgery resulted in significantly longer CSS than targeted therapy alone (P < .001). In multivariable analysis, high Fuhrman grade, size of RPR tumour, mixed type of RPR, multiple recurrence lesions and the absence of RPR surgery were associated with a significantly increased risk of death from RCC, suggesting that an aggressive surgical resection of RPR after RN represents a potentially curative treatment for selected RCC patients without synchronous metastases, resulting in significantly longer CSS than targeted therapy alone [636].

Minimally-invasive approaches, including standard and hand-assisted laparoscopic- and robotic approaches for the resection of isolated RCC recurrences have been occasionally reported. A large surgical cohort published of robotic surgery in this setting (n = 35) providing a standardisation of the nomenclature, describing the surgical technique for each scenario and reporting on complications, renal function, and oncologic outcomes [637]. Ablative therapies including cryoablation, radiofrequency and microwave ablation, may also have a role in managing recurrent RCC patients, but further validation will be needed [638, 639].

In summary, the limited available evidence suggests that in selected patients surgical removal of locally-recurrent disease with negative margins can induce durable tumour control, although with expected high risk of complications. A retrospective review on 51 planned repeat PNs in 47 patients with locally-recurrent disease, reporting a total of 40 peri-operative complications, with temporary urinary extravasation being the most prevalent [640]. Since local recurrences develop early, with a median time interval of 10-20 months after treatment of the primary tumour [641], a guideline-adapted follow-up scheme for early detection is recommended (see Chapter 8 - Follow-up) even though benefit in terms of cancer control has not yet been demonstrated [642].

Adverse prognostic parameters are a short time interval since treatment of the primary tumour (< 3-12 months) [643], sarcomatoid differentiation of the recurrent lesion and incomplete surgical resection [630]. In case complete surgical removal is unlikely to be performed or when significant comorbidities are present (especially when combined with poor prognostic tumour features), palliative therapeutic approaches including radiation therapy aimed at symptom control and prevention of local complications should be considered (see Sections 7.3 and 7.4). Following metastasectomy of local recurrence after nephrectomy, adjuvant therapy can be considered (see Section 7.2.5. Neoadjuvant and adjuvant therapy). Local recurrence combined with other metastases is treated as a metastatic RCC.

7.5.3 Summary of evidence and recommendation on locally-recurrent RCC after treatment of localised disease

Summary of evidence	LE
Isolated recurrence after nephron sparing procedures or nephrectomy is a rare entity (< 2%).	3
Surgical or percutaneous treatment of local recurrences in absence of systemic progression should be considered, especially in absence of adverse prognostic parameters and favourable performance status.	3
The most optimal modality of local treatment for locally-recurrent RCC after nephron sparing procedures or nephrectomy is not defined.	3

Recommendation	Strength rating
Offer local treatment of locally-recurrent disease when technically possible and after balancing adverse prognostic features, comorbidities and life expectancy.	Weak

8. FOLLOW-UP IN RCC

8.1 Introduction

Surveillance after treatment for RCC allows the urologist to monitor or identify:

- post-operative complications;
- renal function;
- local recurrence;
- recurrence in the contralateral kidney;
- distant metastases;
- cardiovascular events.

There is no consensus on follow-up strategies after RCC treatment, with limited evidence suggesting that more frequent post-operative imaging intervals do not provide any improvement for early detection of recurrence that would lead to improved survival [642]. As such, intensive radiological surveillance may not be necessary for all patients. Follow-up is also important to assess functional outcomes and to limit long-term sequelae such as renal function impairment, ESRD and cardiovascular events [644].

Currently, the key question is whether any recurrence detection during follow-up and subsequent treatment will lead to any meaningful change in survival outcome for these patients.

In contrast to high-grade and/or locally-advanced disease, the outcome after surgery for T1a low-grade tumours is almost always excellent. It is therefore reasonable to stratify follow-up, taking into account the risk of each different RCC to develop a local or distant recurrence. Although there is no randomised evidence, large studies have examined prognostic factors with long follow-up [197, 645, 646] (LE: 4). One study has shown a survival benefit in patients who were followed within a structured surveillance protocol vs. patients who were not [647]; patients undergoing follow-up seem to have a longer OS when compared to patients not undergoing routine follow-up [647].

Furthermore, an individualised and risk-based approach to RCC follow-up has recently been proposed. The authors used competing risk models, incorporating patient age, pathologic stage, relapse location and comorbidities, to calculate when the risk of non-RCC death exceeds the risk of RCC recurrence [648]. For patients with low-stage disease but with a Charlson comorbidity index > 2, the risk of non-RCC death exceeded that of abdominal recurrence risk already one month after surgery, regardless of patient age. As for pshylogical factors, a SR including 15 studies revealed that psychological distress (defined as anxiety, depression, or psychological distress at any time during treatment or follow-up) is also prevalent among renal cell carcinoma (RCC) patients, reaching up to 77% in non-metastatic cases [649].

The RECUR consortium, initiated by this Panel, collects similar data with the aim to provide comparators for guideline recommendations. Recently published RECUR data support a risk-based approach; more specifically a competing-risk analysis showed that for low-risk patients, the risk of non-RCC related death exceeded the risk of RCC recurrence shortly after the initial surgery. For intermediate-risk patients, the corresponding time point was reached around four to five years after surgery. In high-risk patients, the risk of RCC recurrence continuously exceeded the risk of non-RCC related death [650]. In the near future, genetic profiling may refine the existing prognostic scores and external validation in datasets from adjuvant trials have been promising in improving stratification of patient's risk of recurrence [650, 651].

Recurrence after PN is rare, but early diagnosis is relevant, as the most effective treatment is surgery [633, 652]. Recurrence in the contralateral kidney is rare (1-2%) and can occur late (median 5-6 years) [653] (LE: 3). Follow-up can identify local recurrences or metastases at an early stage. At recurrence, extensive metastatic tumour growth can hinder the opportunity for surgical resection. In addition, early diagnosis of tumour recurrence may enhance the efficacy of systemic treatment if the tumour burden is low.

8.2 Which imaging investigations for which patients, and when?

- The sensitivity of chest radiography and US for detection of small RCC metastases is poor. The sensitivity of chest radiography is significantly lower than CT-scans, as proven in comparative studies including histological evaluation [654-656]. Therefore, follow-up for recurrence detection with chest radiography and US are less sensitive [657].
- Positron-emission tomography and PET-CT as well as bone scintigraphy should not be used routinely in RCC follow-up, due to their limited specificity and sensitivity [117, 131].
- Surveillance should also include evaluation of renal function and cardiovascular risk factors [644].
- Outside the scope of regular follow-up imaging of the chest and abdomen, targeted imaging should be considered in patients with organ-specific symptoms, e.g., CT or MRI imaging of the brain in patients experiencing neurological symptoms [658].

Controversy exists on the optimal duration of follow-up. Some authors 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. Several authors have designed scoring systems and nomograms to quantify the likelihood of patients to develop tumour recurrences, metastases, and subsequent death [250, 252, 659, 660]. These models, of which the most utilised are summarised in Chapter 6 - Prognosis, have been compared and validated [661] (LE: 2). Using prognostic variables, several stage-based follow-up regimens have been proposed, although, none propose follow-up strategies after ablative therapies [662, 663]. A post-operative nomogram is available to estimate the likelihood of freedom from recurrence at five years [247]. Recently, a pre-operative prognostic model based on age, symptoms and TNM staging has been published and validated [664] (LE: 3). A follow-up algorithm for monitoring patients after treatment for RCC is needed, recognising not only the patient's risk of recurrence profile, but also the efficacy of the treatment given (Table 8.1). These prognostic systems can be used to adapt the follow-up schedule according to predicted risk of recurrence. Ancillary to the above, life-expectancy calculations based on comorbidity and age at diagnosis may be useful in counselling patients on duration of follow-up [665].

Table 8.1: Proposed follow-up schedule following treatment for localised RCC, taking into account patient risk of recurrence profile and treatment efficacy (based on expert opinion [LE: 4])

Risk profile (*)	Oncological follow-up after date of surgery								
	3 mo	**6 mo**	**12 mo**	**18 mo**	**24 mo**	**30 mo**	**36 mo**	**> 3 yr (**) (***)**	**> 5 yr (**) (***)**
Low risk of recurrence For ccRCC: Leibovich Score 0-2 For non-ccRCC: pT1a-T1b pNx-0 M0 and histological grade 1 or2.	-	CT	-	CT	-	CT	-	CT once every two yrs	-
Intermediate risk of recurrence For ccRCC: Leibovich Score 3-5 For non-ccRCC: pT1b pNx-0 and/or histological grade 3 or 4.	-	CT	CT	-	CT	-	CT	CT once yr	CT once every two yrs
High risk of recurrence For ccRCC: Leibovich Score ≥ 6 For non-ccRCC: pT2–pT4 with any histological grade or pT any, pN1 cM0 with any histological grade	CT	CT	CT	CT	CT	-	CT	CT once yr	CT once every two yrs

ccRCC = clear cell renal cell carcinoma; CT = computed tomography; mo = months; non-ccRCC = non clear cell renal cell carcinoma; yr = years.

The table above provides recommendations on follow-up strategies for low, intermediate and high risk of recurrence in patients curatively treated for localised RCC either with NSS or RN. Computed tomography in the table refers to imaging of both chest and abdomen. Alternatively, MRI of the abdomen can be performed instead of a CT-scan.

* *Risk of recurrence profiles should be based on validated prognostic models. The EAU RCC Guidelines Panel recommends the 2003 Leibovich model for ccRCC [250]. However, other validated models can be used by physicians based on their own national/regional recommendations. In a similar fashion, for curatively treated localised non-ccRCC, the Panel recommends the use of the University of California Los Angeles integrated staging system (UISS) to determine risk of recurrence [251].*

** *For all risk of recurrence profiles, functional follow-up, mainly monitoring renal and cardiovascular function, may continue according to specific clinical needs irrespective of the length of the oncological follow-up.*

*** *For low-risk profiles at > 3 years and intermediate-risk at > 5 years of follow-up respectively, consider counselling patients about terminating oncological follow-up imaging based on assessment of comorbidities, age, life expectancy and/or patient wishes.*

8.3 Summary of evidence and recommendations for surveillance following RN or PN or ablative therapies in RCC

Summary of evidence	LE
Functional follow-up after curative treatment for RCC is useful to prevent renal and cardiovascular deterioration.	4
Oncological follow-up can detect local recurrence or metastatic disease while the patient may still be surgically curable.	4
After NSS, there is an increased risk of recurrence for larger (> 7 cm) tumours, or when there is a PSM.	3
Patients undergoing follow-up have a better OS than patients not undergoing follow-up.	3
Prognostic models provide stratification of RCC risk of recurrence based on TNM and histological features.	3
In competing-risk models, risk of non-RCC-related death exceeds that of RCC recurrence or related death in low-risk patients.	3
Life expectancy estimation is feasible and may support counselling of patients on duration of follow-up.	4
Overall survival is reduced in metastatic RCC patients with symptoms of depression and distress.	2a

Recommendations	Strength rating
Base follow-up after treatment of localised RCC on the risk of recurrence.	Strong
Base risk of recurrence stratification on validated subtype-specific models such as the Leibovich Score for clear cell renal cell carcinoma (ccRCC), or the University of California Los Angeles integrated staging system for non-ccRCC.	Weak
Intensify follow-up in patients after nephron-sparing surgery for tumours > 7 cm or in patients with a positive surgical margin.	Weak
Consider curtailing follow-up when the risk of dying from other causes is double that of the RCC recurrence risk.	Weak
Offer psychological evaluation for all patients diagnosed with RCC to provide timely support for distress, depression, or anxiety.	Weak

8.4 Patient involvment in kidney cancer treatment

One RCT has indicated that patient involvement in reporting their symptoms during management of a variety of metastatic solid tumours, can improve clinical outcomes, including OS [666].

A large-scale global survey of patients with renal cell carcinoma (RCC), identified geographic variations in patient education, experience, awareness, access to care, best practices, quality of life, and unmet psychosocial needs [667]. A total of 1,983 patients from 43 countries revealed that at diagnosis, 43% of all respondents had no understanding of their RCC subtype, 29% of all patients reported no involvement in their treatment decision and 96% of respondents reported psychosocial impacts, with only 50% disclosing it to their health care team, with 90% indicated they would be interested in participating in clinical trails.

8.5 Recommendation on patient involvement and shared decision making

Recommendation	Strength rating
Employ a shared decision-making approach when deciding on appropriate treatment for RCC	Strong

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10. CONFLICT OF INTEREST

All members of the Renal Cell Cancer Guidelines Panel have provided disclosure statements of all relationships that they have that might be perceived as a potential source of a conflict of interest. This information is publicly accessible through the European Association of Urology website: https://uroweb.org/guideline/renalcell-carcinoma/?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.

11. CITATION INFORMATION

The format in which to cite the EAU Guidelines will vary depending on the style guide of the journal in which the citation appears. Accordingly, the number of authors or whether, for instance, to include the publisher, location, or an ISBN number may vary.

The compilation of the complete Guidelines should be referenced as:
EAU Guidelines. Edn. presented at the EAU Annual Congress Paris 2024. ISBN 978-94-92671-23-3.

If a publisher and/or location is required, include:
EAU Guidelines Office, Arnhem, The Netherlands. http://uroweb.org/guidelines/compilations-of-all-guidelines/

References to individual guidelines should be structured in the following way:
Contributors' names. Title of resource. Publication type. ISBN. Publisher and publisher location, year.

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

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European Association of Urology

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1. INTRODUCTION

1.1 Aim and scope

This overview represents the updated European Association of Urology (EAU) Guidelines for Non-muscle invasive Bladder Cancer (NMIBC), TaT1 and carcinoma *in situ* (CIS). The information presented is limited to urothelial carcinoma (UC), unless specified otherwise. The aim is to provide practical recommendations on the clinical management of NMIBC with a focus on clinical presentation. Separate EAU Guidelines are available addressing upper tract urothelial carcinoma (UTUC) [1], muscle-invasive and metastatic bladder cancer (MIBC) [2] and primary urethral carcinoma [3].

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

1.2 Panel composition

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

1.3 Available publications

A quick reference document, the Pocket guidelines), is available in print. This is an abridged version which may require consultation together with the full text version. Several scientific publications are available, the latest publication dating to 2022 [4]. All documents are accessible through the EAU website Uroweb: https://uroweb.org/guidelines/non-muscle-invasive-bladder-cancer.

1.4 Publication history and summary of changes

*1.4.1 **Publication history***

The EAU Guidelines on Bladder Cancer were first published in 2000. Standard procedure for EAU Guidelines includes an annual assessment of newly published literature in the field to guide future updates This 2024 NMIBC Guidelines present a limited update of the 2023 publication.

*1.4.2 **Summary of changes***

For the 2024 NMIBC Guidelines new and relevant evidence was identified, collated and appraised through a structured assessment of the literature for all sections of the Guidelines. This resulted in the inclusion of 36 updated studies across the Guidelines. Key changes include the addition of:

- a new category of high-grade recurrence during or after BCG (table 7.2): the BCG-exposed tumour category;
- updates on the proposed treatment options for late BCG relapses and low grade (LG) recurrence after bacillus Calmette-Guérin (BCG) for primary intermediate-risk bladder cancer in table 7.3;
- a proposed follow-up schedule based on patient's risk category in Table 8.2;
- a new section on patient reported outcome measures and quality indicators for NMIBC (section 9).

In addition, minor adaptions and updates to multiple recommendations have been made and users are advised to review all sections in full. A summary of key recommendation changes include:

- an update in the evidence and guidelines in section 4.10 on bladder cancer classification;
- new summary of evidence and recommendations updates in section 5.15 on the transurethral resection of the bladder, biopsies and pathology report;
- guidelines updates in section 7.10 on adjuvant therapy in TaT1 tumours and for therapy of carcinoma *in situ*;
- a new update to the very high risk EAU risk group, in section 7.11 on the guidelines for the treatment of TaT1 tumours and carcinoma *in situ* according to risk stratification;

- new updates in section 8.2 on the summary of evidence and recommendations for the follow-up of patients after transurethral resection of the bladder for non-muscle-invasive bladder cancer.

2. METHODS

2.1 Data Identification

For the 2024 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. Databases searched included Medline, EMBASE, and the Cochrane Libraries, covering a time frame between the 5th of May 2022 and 1st May 2023. A total of 788 unique records were identified, retrieved, and screened for relevance. A total of 36 new references were added to the 2024 NMIBC Guidelines. A detailed search strategy is available online: https://uroweb.org/guidelines/non-muscle-invasive-bladder-cancer/publications-appendices.

For Chapters 3 through 6 (Epidemiology, Aetiology and Pathology, Staging and Classification systems, Diagnosis, Predicting disease recurrence and progression) the references used in this text were assessed according to their level of evidence (LE) based on the 2009 Oxford Centre for Evidence-Based Medicine (CEBM) Levels of Evidence [5]. For chapters 7 and 8 (Disease Management and Follow-up) chapters a system modified from the 2009 CEBM levels of evidence was used [5].

Recommendations within the Guidelines are developed by the panels to prioritise clinically important care decisions. The strength of each recommendation is determined by the balance between desirable and undesirable consequences of alternative management strategies, the quality of the evidence (including certainty of estimates), and the nature and variability of patient values and preferences. This decision process, which can be reviewed in the strength rating forms which accompany each guideline statement, addresses a number of key elements:

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

Strong recommendations typically indicate a high degree of evidence quality and/or a favourable balance of benefit to harm and patient preference. Weak recommendations typically indicate availability of lower quality evidence, and/or equivocal balance between benefit and harm, and uncertainty or variability of patient preference [6].

Additional methodology information and a list of associations endorsing the EAU Guidelines can be found in the online: https://uroweb.org/eau-guidelines/methodology-policies.

2.2 Review

The 2024 publication was peer reviewed prior to publication.

2.3 Future goals

The Panel are currently conducting two individual patient data (IPD) analyses to validate the definition of bacillus Calmette-Guérin (BCG) failure/BCG unresponsive in patients with non-muscle invasive urothelial carcinoma of the bladder and the impact of BCG on progression in the BCG treated subgroup of the original cohort that served to generate the 2021 risk stratification. The results of both analyses will be included in the future update of the NMIBC Guidelines.

3. EPIDEMIOLOGY AND AETIOLOGY

3.1 Epidemiology

Bladder cancer (BC) is the seventh most commonly diagnosed cancer in the male population worldwide, and it is the tenth when both genders are considered [7]. The worldwide age-standardised incidence rate (per 100,000 person/years) is 9.5 in men and 2.4 in women [7]. In the European Union, the age-standardised incidence rate is 20 in men and 4.6 in women [7].

Worldwide, the BC age-standardised mortality rate (per 100,000 person/years) is 3.3 for men vs. 0.86 for women [7]. Bladder cancer incidence and mortality rates vary across countries due to differences in risk factors, detection and diagnostic practices, and variations in access to, and delivery of, healthcare. Additionally, epidemiological variations have been attributed to differing methodologies and the quality of data from individual datasets [8]. The incidence and mortality of BC has decreased in some registries, possibly reflecting the decreased impact of causative factors [9].

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

3.2 Aetiology

*3.2.1 **Main risk factors***

3.2.1.1 Tobacco

Tobacco smoking is the most important risk factor for BC, accounting for approximately 50% of cases [8, 9, 11, 12]. The aromatic amines and polycyclic aromatic hydrocarbons within the tobacco smoke, which undergo renal excretion, are linked to the development of BC. The risk of BC increases with smoking duration and intensity [18]. Low-tar cigarettes are not associated with a lower risk of developing BC [13]. The risk associated with electronic cigarettes has not been adequately assessed; however, carcinogens have been identified in the urine with electronic cigarettes [14]. 'Second-hand' exposure to tobacco smoke is also associated with an increased risk of BC [8].

3.2.1.2 Occupational exposure

Occupational exposure to aromatic amines, polycyclic aromatic hydrocarbons and chlorinated hydrocarbons is the second most important risk factor for BC, accounting for about 10% of all cases. This type of occupational exposure occurs mainly in industrial plants which process paint, dye, metal, and petroleum products [8, 9, 15, 16]. In developed industrial settings these risks have been reduced by work-safety guidelines; therefore, chemical workers no longer have a higher incidence of BC compared to the general population [8, 15, 16]. Recently, greater occupational exposure to diesel exhaust has been suggested as a significant risk factor (odds ratio [OR]: 1.61; 95% confidence interval [CI]: 1.08–2.40) [17]. Additionally, a large registry-based study of over one million people, with a follow up of 21 years, found that residents in the Haifa Bay Area of Israel (which is a centre for petrochemical industry) had a significantly higher incidence of several cancers, including bladder cancer (hazard ratio [HR] 1.11; 95% CI: 1.01–1.23), compared with non-residents [18].

*3.2.2 **Genetic***

Family history seems to have little impact [19]. To date, no clinically relevant genetic alteration has been linked to BC. Genetic predisposition may lead to a higher susceptibility to other risk factors, and thereby explain the familiar clustering of BC in first- and second-degree relatives (HR: 1.69; 95% CI: 1.47–1.95) [8, 20-25] that has been confirmed more recently [26]. A recent study identified three single nucleotide polymorphisms related to the development of aggressive NMIBC [27]. Currently, there is insufficient evidence to support genetic screening for BC.

*3.2.3 **Dietary habits***

Dietary habits seem to have limited impact on the risk of developing BC. A protective impact of flavonoids has been suggested [28]. The Mediterranean diet, characterised by a high consumption of vegetables and non-saturated fat (olive oil) with moderate consumption of protein, has been linked to some reduction of BC risk (HR: 0.85; 95% CI: 0.77–0.93) [29-33]. Western diet (high in saturated fats) and organ meat has been shown to increase the risk of BC in a recent meta-analysis [34, 35]. The impact of an increased consumption of fruits has been suggested to reduce the risk of BC. This effect has been demonstrated to be significant in women only (HR: 0.92; 95% CI: 0.85–0.99) [36]. This gender discrepancy was also evident in the BLEND study which showed that in men moderate or high intake of vitamins B1, B2 and vitamins related to energy metabolism were found to be associated with an increased BC risk, whereas in women high intake of the same vitamins and vitamin combinations was shown to have a protective effect with the exception of the entire B group vitamin

complex [37]. One possible explanation for this gender discrepancies is the difference in the main source of vitamin intake among study participants, being meat in men and fruits/vegetables in women. In addition, higher consumption of tea has also been associated with a reduction in risk of BC in men but through an interaction with tobacco smoking; therefore, making the protective effect of this compound questionable [38].

*3.2.4 **Environmental exposure***

Although the impact of drinking habits remains uncertain, the chlorination of drinking water and subsequent levels of trihalomethanes are potentially carcinogenic. Additionally, exposure to arsenic in drinking water has been suggested to increase the risk of BC [8, 39]. Arsenic intake and smoking have a combined effect [40]. Conversely, chronic exposure to nitrate in drinking water does not seem to be associated with increased risk of BC [41].

The association between personal hair dye use and risk of BC remains uncertain; an increased risk has been suggested in users of permanent hair dyes with a slow NAT2 acetylation phenotype [8] but a large prospective cohort study could not identify an association between hair dye and risk of cancer and cancer-related mortality [42].

*3.2.5 **Pelvic radiation***

Exposure to pelvic ionizing radiation is associated with an increased risk of BC [43, 44]. In a retrospective analysis of patients with localised prostate cancer, external beam radiotherapy (EBRT) was independently associated with a risk of developing a second primary BC [43]. A single centre study of 583 prostate cancer patients treated with brachytherapy revealed that the risk of developing BC increased in those who received additional EBRT (n=255) (HR 3.29; 95% CI 1.03–10.52). The BC specific mortality was also higher when combination therapy was used [44].

*3.2.6 **Other***

The impact of metabolic factors (body mass index, blood pressure, plasma glucose, cholesterol, and triglycerides) remains uncertain [45]. However, data suggest that high circulating levels of vitamin D are associated with a reduction in the risk of BC [46]. Schistosomiasis, which is an infection caused by a parasitic trematode, can lead to BC [8]. A weak association was also suggested for cyclophosphamide and pioglitazone [8, 39, 47].

3.3 Summary of evidence for epidemiology and aetiology

Summary of evidence	**LE**
Worldwide, bladder cancer (BC) is the tenth most commonly diagnosed cancer.	2a
Several risk factors connected with the risk of BC diagnosis have been identified.	3
Tobacco smoking is the most important risk factor for BC.	3

4. PATHOLOGICAL STAGING, GRADING AND CLASSIFICATION SYSTEMS

4.1 Definition of non-muscle-invasive bladder cancer

Urothelial 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 [48]. Intra-epithelial, high-grade (HG) tumours confined to the mucosa are classified as CIS (Tis). All of these tumours can be treated by transurethral resection of the bladder (TURB), eventually in combination with intravesical instillations and are therefore grouped under the heading of NMIBC for therapeutic purposes. The term 'Non-muscle-invasive BC' represents a group definition and all tumours should be characterised according to their stage, grade, and further pathological characteristics (see Sections 4.5 and 4.7 and the International Collaboration on Cancer Reporting website: http://www.iccr-cancer.org/datasets/published-datasets/urinary-male-genital/bladder. The term 'superficial BC' should no longer be used as it is incorrect.

4.2 Tumour, Node, Metastasis Classification (TNM)

The latest TNM classification approved by the Union International Contre le Cancer (UICC) (8th Edn.) is referred to (Table 4.1) [48].

Table 4.1: 2017 TNM classification of urinary bladder cancer

T - Primary tumour		
TX	Primary tumour cannot be assessed	
T0	No evidence of primary tumour	
Ta	Non-invasive papillary carcinoma	
Tis	Carcinoma *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 regional lymph nodes in the true pelvis (hypogastric, obturator, external iliac, or presacral)	
N3	Metastasis in common iliac lymph node(s)	
M - Distant metastasis		
M0	No distant metastasis	
	M1a	Non-regional lymph nodes
	M1b	Other distant metastases

4.3 T1 subclassification

The depth and extent of invasion into the lamina propria (T1 sub-staging) has been demonstrated to be of prognostic value in retrospective cohort studies [48, 49] (LE: 3). Its use is recommended by the most recent 2022 World Health Organization (WHO) classification [50, 51]. T1 sub-staging methods are based either on micrometric (T1e and T1m) or histo-anatomic (T1a and T1b) principles; the optimal classification system, however, remains to be defined [52, 53] .

4.4 Lymphovascular invasion

The presence of lymphovascular invasion (LVI) in TURB specimens is associated with an increased risk of pathological upstaging and worse prognosis [54-58] (LE: 3). Immunohistochemistry for confirmation is not mandatory [50].

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

4.5.1 Types of histological grading systems

In 2004 the WHO published a histological classification system for UCs including papillary urothelial neoplasm of low malignant potential (PUNLMP), non-invasive papillary carcinoma low grade (LG) and HG. This system was also taken into the updated 2016/2022 WHO classifications [50, 51]. It provides a different patient stratification between individual categories compared to the older 1973 WHO classification, which distinguished between grade 1 (G1), grade 2 (G2) and grade 3 (G3) categories [52, 59].

There is a significant shift of patients between the categories of the WHO 1973 and the WHO 2004/2022 systems (see Figure 4.1), for example an increase in the number of HG patients (WHO 2004/2022) due to inclusion of a subset of G2 patients with a more favourable prognosis compared to the G3 category (WHO 1973) [60, 61]. According to a multi-institutional individual patient data analysis, the proportion of tumours classified as PUNLMP (WHO 2004/2016) has decreased to very low levels in the last decade [62].

4.5.2 Prognostic value of histological grading

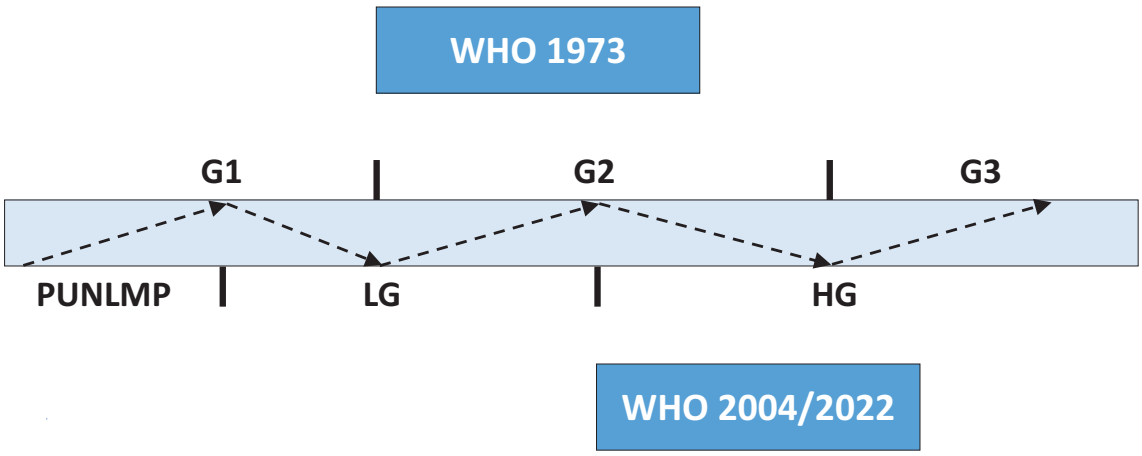
A systematic review and meta-analysis did not show that the 2004/2016 classification outperforms the 1973 classification in prediction of recurrence and progression [60].

To compare the prognostic value of both WHO classifications, an individual patient data analysis of 5,145 primary TaT1 NMIBC patients from sixteen centres throughout Europe and one in Canada was conducted. Patients had a transurethral resection of bladder tumour (TURBT) followed by intravesical instillations at the physician's discretion. In this large study, the WHO 1973 and the WHO 2004/2016 were both prognostic for progression but not for recurrence. When compared, the WHO 1973 was a stronger prognosticator of progression in TaT1 NMIBC than the WHO 2004/2016. However, a 3-tier (LG/G1-G2, HG/G2 & HG/G3) or a 4-tier hybrid combination LG/G1, LG/G2, HG/G2 and HG/G3) of both classification systems proved to be superior to either classification system alone, as it divides the large group of G2 patients into two subgroups (LG/HG) with different prognoses [63]. In a subgroup of 3,311 patients with primary Ta bladder tumours, a similar prognosis was found for PUNLMP and Ta LG carcinomas [62].

4.5.3 Clinical application of histological grading systems

- The WHO 2004/2022 classification system is currently supported by the WHO for clinical application. Nevertheless, the WHO 1973 is still being used.
- The most important parameters, which must be considered for clinical application of any grading system are its inter-observer reproducibility and prognostic value (see Sections 4.5.1 and 4.6).
- These guidelines provide recommendations for tumours classified by both classification systems.

Figure 4.1: Schematic representation of tumours according to grade in the WHO 1973 and 2004/2022 classifications [63]*



**Grade shifts from the WHO 1973 (G1–G3) to the WHO 2004/2022 (PUNLMP, LG and HG) classification for Ta/T1 bladder tumours are displayed with dotted lines and arrows. Along the dotted lines, both the degree of anaplasia and the 5-year progression rates increased in LG/G1, LG/G2, HG/G2, and HG/G3 patients.*

Note: the 2004/2022 WHO classification is the updated version of 2004/2016 WHO classification. According to a series of 5145 primary Ta-T1 patients, the distribution of G1, G2 and G3 in the WHO 1973 classification is 23.5, 49.3 and 27.2% respectively while the corresponding PUNLMP, LG and HG rates for the WHO 2004/2022 system are 1.5, 49.8 and 48,7% respectively [63]. Figure reproduced with permission from Elsevier from [63] .

4.6 Carcinoma *in situ*

Carcinoma *in situ* is an intra-epithelial, HG, non-invasive UC. It can be missed or misinterpreted as an inflammatory lesion during cystoscopy if not biopsied. Carcinoma *in situ* is often multifocal and can occur in the bladder, but also in the upper urinary tract (UUT), prostatic ducts and urethra [64].

From a clinical point of view, CIS may be classified as [65]:

- 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.

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

There is significant variability among pathologists for the diagnosis of CIS, for which agreement is achieved in only 70–78% of cases [66]. There is also inter-observer variability in the classification of stage T1 vs. Ta tumours and tumour grading in both the 1973 and 2022 classifications. The general conformity between pathologists in staging and grading is 50–60% [67-70]. The WHO 2004/2022 classification provides slightly better reproducibility than the 1973 classification [60].

4.8 Subtypes of urothelial carcinoma

Currently the following differentiations of urothelial carcinoma (UC) are used [71, 72]:

1. Pure UC (more than 90% of all cases);
2. UC with partial (squamous-glandular or trophoblastic) divergent differentiation;
3. UC with micropapillary divergent differentiation;
4. UC with nested/microcystic divergent differentiation;
5. UC with microtubular divergent differentiation;
6. UC with large nested divergent differentiation;
7. UC with plasmacytoid divergent differentiation;
8. UC with lymphoepithelioma-like divergent differentiation;
9. UC with giant cell, diffuse, undifferentiated divergent differentiation;
10. UC with sarcomatoid divergent differentiation;
11. some UCs with other rare differentiations;
12. UCs with partial NE (neuroendocrine differentiation, % to be given);
13. pure neuroendocrine carcinoma (including small and large cell neuroendocrine carcinomas.

In the new WHO 2022 all subtypes are considered HG [51]. The percentage of subtype in the specimen should be reported since it has been shown to be of prognostic value [73]. The WHO 2022 classification considers all subtypes UC (LG and HG) with more than 5% of HG as a HG tumour [2, 73-80].

4.9 Tumour markers and molecular classification

Tumour markers and their prognostic role have been investigated [81-85]. These methods, in particular complex approaches such as the stratification of patients based on molecular classification, are promising but have not yet been recommended by any pathological organisation and are therefore not suitable for routine application [53, 86, 87].

4.10 Summary of evidence and guidelines for bladder cancer classification

Summary of evidence	**LE**
The depth of invasion (staging) is classified according to the TNM classification.	2a
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
Histological grading of urothelial NMIBC is classified according to the WHO 2004/2016/2022 (PUNLMP, LG/HG) systems and/or WHO 1973 (G1–G3).	2a
The WHO 2004/2016/2022 classification provides slightly better reproducibility than the 1973 classification.	2a

Both the WHO 1973 and the 2004/2016/2022 classification systems are prognostic for progression, but not for recurrence.	2a
The WHO 1973 is a stronger prognosticator of progression in TaT1 NMIBC than the WHO 2004/2016. However, a 3-tier hybrid (LG/G1-G2, HG/G2 & HG/G3) or a 4-tier hybrid LG/G1, LG/G2, HG/G2 and HG/G3) combination of both classification systems proved to be superior to either classification system alone.	2a

Recommendations	Strength rating
Use the 2017 TNM system for classification of the depth of tumour invasion (staging).	Strong
Provide T1 sub-stage if the lamina propria is adequately sampled using either micrometric (T1e and T1m) or histo-anatomic (T1a and T1b) principles.	Weak
Use both the 1973 and 2004/2022 WHO grading classification systems, or a hybrid system.	Weak
Do not use the term 'superficial' bladder cancer.	Strong

5. DIAGNOSIS

5.1 Patient history

A focused patient history is mandatory.

5.2 Signs and symptoms

Haematuria is the most common finding in NMIBC. Visible haematuria was found to be associated with higher stage at diagnosis disease compared to nonvisible haematuria [88]. Carcinoma *in situ* might be suspected in patients with lower urinary tract symptoms, especially irritative voiding symptoms.

5.3 Physical examination

A focused urological examination is mandatory although it does not reveal NMIBC.

5.4 Imaging

*5.4.1 **Computed tomography urography and intravenous urography***

Computed tomography (CT) urography is used to detect papillary tumours in the urinary tract, indicated by filling defects and/or hydronephrosis [89].

Intravenous urography (IVU) is an alternative if CT is not available [90], but CT urography provides more information particularly in muscle-invasive tumours of the bladder and in UTUCs (including status of lymph nodes and neighbouring organs).

The necessity to perform a baseline CT urography once a bladder tumour has been detected is questionable due to the low incidence of significant findings which can be obtained [91-93]. The incidence of UTUCs is low (1.8%), but increases to 7.5% in tumours located in the trigone [92]. The risk of UTUC during follow-up increases in patients with multiple and high-risk tumours [94].

*5.4.2 **Ultrasound***

Ultrasound (US) may be performed as an adjunct to physical examination as it has moderate sensitivity to a wide range of abnormalities in the upper- and lower urinary tract. It permits characterisation of renal masses, detection of hydronephrosis, and visualisation of intraluminal masses in the bladder, but cannot rule out all potential causes of haematuria [95, 96]. It cannot reliably exclude the presence of UTUC and cannot replace CT urography.

*5.4.3 **Multi-parametric magnetic resonance imaging***

The role of multi-parametric magnetic resonance imaging (mpMRI) has not yet been established in BC diagnosis and staging. A standardised methodology of MRI reporting (Vesical Imaging-Reporting and Data System [VI-RADS]) in patients with BC has recently been published and requires further validation [97]. A systematic review of 8 studies showed that the VI-RADS scoring system can accurately differentiate NMIBC from MIBC with high inter-observer agreement rates [98]. A diagnosis of CIS cannot be made with imaging methods alone (CT urography, IVU, US or MRI).

5.5 Urinary cytology

The examination of voided urine or bladder-washing specimens for exfoliated cancer cells has high sensitivity in HG and G3 tumours (84%), but low sensitivity in LG/G1 tumours (16%) [99]. The sensitivity in CIS detection is 28–100% [100]. A recent report applying the Paris system found a sensitivity of 46% for HG disease [101]. Cytology is useful, particularly as an adjunct to cystoscopy, in patients with HG/G3 tumours; it is not designed to detect LG tumours. Positive voided urinary cytology can indicate an UC anywhere in the urinary tract; negative cytology, however, does not exclude its presence.

Cytological interpretation is user-dependent [102, 103] and evaluation can be hampered by low cellular yield, urinary tract infections, stones, or intravesical instillations: although in experienced hands specificity exceeds 90% [104]. Artificial intelligence algorithms combined with digital image processing (VisioCyt test) improved the sensitivity of cytology for HG tumours up to 92% [105].

A standardised reporting system known as The Paris System published in 2022 (2nd Edn.) redefined urinary cytology diagnostic categories as follows [106]:

- No adequate diagnosis possible (No diagnosis);
- Negative for UC (Negative);
- Atypical urothelial cells (Atypia);
- Suspicious for HG UC (Suspicious);
- High-grade/G3 UC (Malignant).

The principle of the system and its terminology underlines the role of urinary cytology in detection of G3 and HG tumours. The Paris system for reporting urinary cytology has been validated in several retrospective studies [107, 108].

Urine collection should respect the recommendation provided in Section 5.9. One cytospin slide from the sample is usually sufficient [106]. In patients with suspicious cytology repeat investigation is advised as the underlying risk of a high grade lesion is between 24-53% [109].

5.6 Urinary molecular marker tests

Driven by the low sensitivity of urine cytology in LG/G1 tumours, numerous urinary tests have been developed [110]. None of these markers have been accepted as routine practice by any clinical guidelines for diagnosis or follow-up.

The following general statements can be drawn regarding the existing tests:

- Sensitivity is usually higher at the cost of lower specificity compared to urine cytology [106].
- Benign conditions and previous BCG instillations may influence the results of many urinary marker tests [111].
- Requirements for sensitivity and specificity of a urinary marker test largely depend on the clinical context of the patient (screening, primary detection, follow-up [high-risk, low/intermediate-risk]) [106].
- Several urinary biomarkers, assessing multiple targets, have been tested in prospective multicentre studies [112, 113]. Four of the commercially available urine biomarkers, Cx-Bladder [114, 115], ADX-BladderTM [116, 117], Xpert Bladder® [118-120] and EpiCheckTM [112], although not tested in RCTs, have such high sensitivities and negative predictive values in the referenced studies for HG disease that these biomarkers may approach the sensitivity of cystoscopy. These 4 tests might be used in the initial diagnostic workup to avoid/implement cystoscopy [114, 121, 122], or in follow-up to replace or postpone cystoscopy [116, 117, 120, 123]. See section 8 for more details on the use of urine markers in the follow up.
- In patients with negative cystoscopy and upper tract work-up, positive results of urine cytology or molecular urine tests such as UroVysion™ (FISH), Nuclear Matrix Protein (NMP)22®, Fibroblast Growth Factor Receptor (FGFR)3/Telomerase Reverse Transcriptase (TERT) and microsatellite analysis may identify patients more likely to experience disease recurrence and possibly progression [124-131].

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, followed by FGFR3, or UroVysionTM tests if dipstick is positive has been reported in BC screening in high-risk populations [132, 133]. However, the low incidence of BC in the general population and the short lead-time impair feasibility and cost-effectiveness of BC screening [127, 133]. Thus, routine screening for BC is not recommended [127, 132, 133].

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

It is generally accepted that none of the currently available tests can replace cystoscopy. However, urinary cytology or biomarkers can be used as an adjunct to cystoscopy to detect missed tumours, particularly CIS. In this setting, specificity is particularly important. Recently, CellDetect® and UroVysion™ have shown similar performance to detect BC and were both superior to cytology [134]. In addition, Xpert Bladder® had higher sensitivity and negative-predictive value than both cytology or UroVysion™ for the detection of BC in patients with haematuria [121].

5.7.3 ***Follow-up of non-muscle-invasive bladder cancer***

The current status of urine cytology and urinary molecular marker tests in follow-up for non-muscle-invasive bladder cancer is discussed in Section 8.

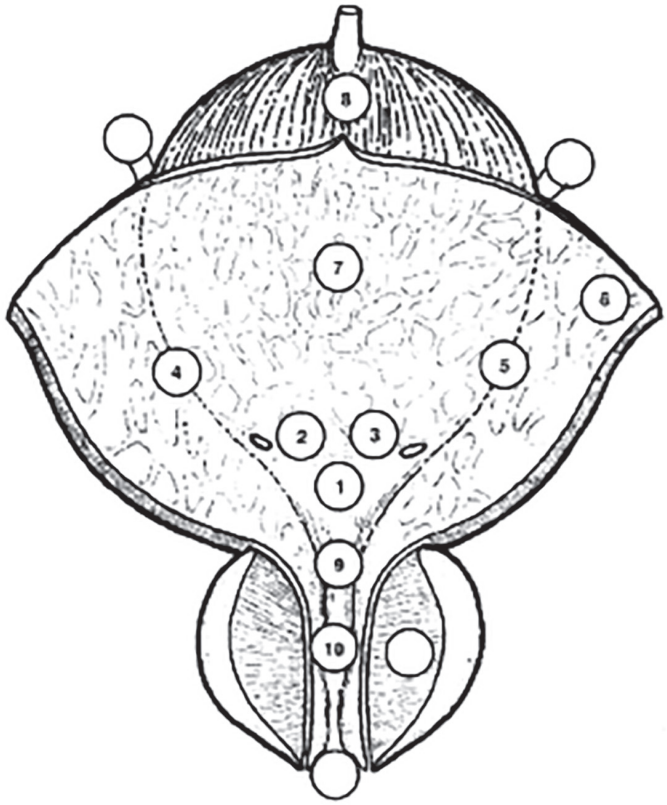
5.8 Cystoscopy

The diagnosis of papillary BC ultimately depends on cystoscopic examination of the bladder and histological evaluation of sampled tissue by either cold-cup biopsy or resection. Carcinoma *in situ* can be suspected through cystoscopy and urine cytology and confirmed by histological evaluation of multiple bladder biopsies [135].

Cystoscopy can be performed as an outpatient procedure. A flexible instrument with topical intraurethral anaesthetic lubricant instillation results in better compliance compared to a rigid instrument, especially in men [136, 137].

To temporary increase the urethral pressure by irrigation 'bag squeeze' when passing membranous and prostatic urethra with a flexible cystoscope in males also decreases pain during the procedure [138, 139].

Figure 5.1: Bladder diagram



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

Summary of evidence	LE
Cystoscopy is necessary for the diagnosis of BC.	1
Urinary cytology has high sensitivity in high-grade tumours including carcinoma *in situ*.	2b

Recommendations	Strength rating
Take a patient history, focusing on urinary tract symptoms and haematuria.	Strong
Use renal and bladder ultrasound and/or computed tomography-intravenous urography (CT-IVU) during the initial work-up in patients with haematuria.	Strong
Once a bladder tumour has been detected, perform a CT urography in selected cases (e.g., tumours located in the trigone, multiple- or high-risk tumours).	Strong
Perform cystoscopy in patients with symptoms suggestive of bladder cancer or during surveillance. It cannot be replaced by cytology or by any other non-invasive test.	Strong
In men, use a flexible cystoscope, if available, and apply irrigation 'bag squeeze' to decrease procedural pain when passing the proximal urethra.	Strong
Describe all macroscopic features of the tumour (site, size, number, and appearance) and mucosal abnormalities during cystoscopy. Use a bladder diagram (Figure 5.1).	Strong
Use voided urine cytology as an adjunct to cystoscopy to detect high-grade tumour.	Strong
Perform cytology on at least 25 mL fresh urine or urine with adequate fixation. First morning urine is not suitable because of the frequent presence of cytolysis.	Strong
Use the Paris System 2nd Edn. for cytology reporting.	Strong

5.10 Transurethral resection of TaT1 bladder tumours

*5.10.1 **Strategy of the procedure***

The goals of TURB in TaT1 BC is to establish accurate pathological diagnosis/staging and completely remove all visible lesions. It is a crucial procedure in the management of BC. Transurethral resection of the bladder tumours should be performed systematically in individual steps [140, 141] (see Section 5.14).

The operative steps necessary to achieve a successful TURB include identifying the factors required to assign disease risk (number of tumours, size, architecture, location, concern for the presence of CIS, recurrent vs. primary tumour), clinical stage (bimanual examination under anaesthesia, assignment of clinical tumour stage), adequacy of the resection (visually complete resection, visualisation of muscle at the resection base), visualisation of tumour in the distal ureter and presence of complications (assessment for perforation) [140, 142]. Documentation of cystoscopic tumour characteristics and consequent clinically predicted tumour grade and stage can help assign patients to post-TURB single instillation of chemotherapy (low grade non-invasive) and muscle invasive cancers to be fast tracked to definitive treatment [143]. To measure the size of the largest tumour, one can use the end of the cutting loop, which is approximately 1 cm wide, as a reference. Tumour architecture can be sessile, nodular, papillary, mixed papillary/solid or flat.

*5.10.2 **Surgical and technical aspects of tumour resection***

5.10.2.1 Surgical strategy of resection (piecemeal/separate resection, en-bloc resection)

A complete resection, performed by either fractioned or *en-bloc* technique, is essential to achieve a good prognosis [141, 144].

- Piecemeal resection in fractions (separate resection of the exophytic part of the tumour, the underlying bladder wall and the edges of the resection area) provides good information about the vertical and horizontal extent of the tumour [145]. Whilst this technique is carried out using a loop with diathermy (monopolar or bipolar), the Thulium-YAG laser is potentially a feasible alternative [146].
- *En-bloc* resection using monopolar or bipolar current, Thulium-YAG or Holmium-YAG or KTP-Green Light lasers is feasible in selected exophytic tumours. It provides high-quality resected specimens with the presence of detrusor muscle in 96–100% of cases [141, 147-154]; however, its superiority over conventional TURB remains debatable [155, 156]. Detrusor muscle sampling rates were no different between these techniques in a systematic review of 1,142 patients [157], and in a single centre RCT showing similar detrusor muscle sampling rates of 95% between conventional TURB and *en-bloc* resection [155]. Conversely, another systematic review of 4,484 patients revealed higher detrusor muscle sampling

rates in favour of *en-bloc* resection [147], and a multicentre RCT found significantly higher detrusor muscle rates with *en-bloc* compared to conventional TURB (80.7 vs 71.1) [156]. Respect for tumour architecture increases the accuracy of T1 staging and the possibility of sub-staging while potentially reducing the risk of bladder perforation [147, 152-155]. With regards oncological outcomes, two RCTs did not reveal a difference in time to recurrence between *en-bloc* resection and conventional TURB [155, 156]. This has also been shown in two systematic reviews [147, 157].

The technique selected is dependent on the size and location of the tumour and experience of the surgeon. The tumour size feasible for retrieval *en-bloc* is limited by the currently available endoscopic equipment and it has been shown that technical success declines with tumours larger than three cm [158]. With better detection of tumours and abnormal margins, methods of optical enhancement are expected to improve complete resection rates (see Section 5.11).

5.10.2.2 Evaluation of resection quality

The absence of detrusor muscle in the specimen is associated with a significantly higher risk of residual disease, early recurrence, and tumour under-staging [159] (LE: 1b). The presence of detrusor muscle in the specimen is considered as a surrogate criterion of the resection quality [159] and is required (except in Ta LG/ G1 tumours). Surgical checklists and quality performance indicator programmes have been shown to increase surgical quality (accurate documentation of factors required to assign risk and sample detrusor muscle) and decrease recurrence rates [140, 142, 160-162]. The Panel have included a sample TURB checklist in Table 5.1 and reported quality indicators for the procedure in Table 9.1.

It has been shown that surgical experience can improve TURB results, which supports the role of teaching programmes [159, 163]. Virtual training on simulators is an emerging approach [164]. Its role in the teaching process still needs to be established [140]. Surgical experience and/or volume has been associated with risk of complications [165], recurrence [166] and survival [167] in retrospective studies. Despite a relatively low overall rate of detrusor muscle (DM) sampling, a collaborative study of 503 patients demonstrated that higher utilisation of surgical checklists by residents was associated with a higher rate of detrusor muscle sampling (62.9%) vs. 'experts' (50.6%) who's utilisation of checklists was lower [140, 162].

5.10.2.3 Monopolar and bipolar resection

Compared to monopolar resection, bipolar resection has been introduced to reduce the risk of complications (e.g., bladder perforation due to obturator nerve stimulation) and to produce better specimens. Currently, the results remain controversial [168-170], with significant inherent limitations due to selection bias, heterogeneity of surgical approach or inability to qualify surgeon experience. A systematic review of 13 RCTs (2,379 patients) showed no benefit of bipolar vs. monopolar TURB for efficacy and safety [170] while one meta-analysis of RCTs (n = 2,099) suggests a lower fall in haemoglobin and shorter hospital stay with bipolar resections [168] and another systematic review of RCTs and observational studies (n = 19,927) suggests lesser thermal artifacts in the specimen [169].

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

It is not uncommon to incidentally detect bladder tumours during TURP in men with benign prostatic hyperplasia. Provided these tumours are papillary, rather small and not extensively multifocal, it seems feasible to resect these tumours and continue with the resection of the prostate [171, 172]. Simultaneous TURB and TURP does not appear to lead to any increased risk of tumour recurrence or progression [173]. Whilst most reports have suggested surgeons prefer to undertake saline irrigation following the combined TURBT and TURP, post-operative single instillation of chemotherapy also appears to be feasible and safe provided there is no capsular or bladder perforation [174].

5.11 Endoscopic biopsies

*5.11.1 **Bladder 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, biopsies from suspicious urothelium should be taken. In patients with positive urine cytology (see Section 5.5), and normal-looking mucosa at cystoscopy, mapping biopsies are recommended [175, 176]. To obtain representative mapping of the bladder mucosa, biopsies should be taken from the trigone, bladder dome, right, left, anterior and posterior bladder wall [175, 176]. If the equipment is available, photodynamic diagnosis (PDD) is a useful tool to target the biopsy (see section 5.12.1).

*5.11.2 **Prostatic urethral biopsies***

Involvement of the prostatic urethra and ducts in men with NMIBC has been reported. Palou *et al.*, showed that in 128 men with T1G3 UC, the incidence of CIS in the prostatic urethra was 11.7% [177]. The risk of prostatic urethra or duct involvement is higher if the tumour is located at the trigone or bladder neck, in the presence of bladder CIS and multiple tumours [178]. Based on this observation, a biopsy from the prostatic urethra is necessary in some cases [177, 179, 180]. Biopsies should preferably be from the pre-collicular area (between 5 and 7 o'clock position next to the veru montanum) using a resection loop.

5.12 New methods of tumour visualisation

As a standard procedure, cystoscopy and TURB are performed using white light (WL). However, the use of WL alone 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 or blue light cystoscopy)***

Photodynamic diagnosis is performed using blue light after intravesical instillation of 5-aminolaevulinic acid (ALA) or hexaminolaevulinic acid (HAL).

5.12.1.1 Impact on bladder cancer detection

It has been confirmed that fluorescence-guided biopsy and resection are more sensitive than conventional procedures for the detection of malignant tumours, particularly CIS [181, 182] (LE: 1a). In a systematic review and meta-analysis, PDD had higher sensitivity than WL endoscopy in the pooled estimates for analyses at both the patient-level (92% vs. 71%) and biopsy-level (93% vs. 65%) [182]. A prospective RCT did not confirm a higher detection rate in patients with known positive cytology before TURB [183].

Photodynamic diagnosis had lower specificity than WL endoscopy (63% vs. 81%) and it does not help to rule out prostatic involvement [182]. False- positivity can be induced by inflammation or recent TURB and during the first 3 months after BCG instillation [184, 185].

5.12.1.2 Impact on bladder cancer recurrence

The beneficial effect of ALA or HAL fluorescence cystoscopy on recurrence rate in patients with TURB was evaluated. A systematic review and analysis of 14 RCTs including 2,906 patients, 6 using 5-ALA and 9 HAL, demonstrated a decreased risk of BC recurrence in the short and long term. There were, however, no differences in progression and mortality rates. The analysis demonstrated inconsistency between trials and potential susceptibility to performance and publication bias [186]. While a recent systematic review and meta-analysis of 12 RCTs (n = 2,288) revealed lower risk of recurrence and improved time to recurrence (at least in the first 2 years and possibly up to 5 years) with PDD [187], the most recent Cochrane systematic review and meta-analysis of 16 RCTs (n = 4,325) demonstrated that PDD-assisted TURBT may prolong not only recurrence over time but also risk of progression, albeit supported only by low certainty evidence [188]. This finding has been corroborated in a systematic review and meta-analysis of 12 RCTs involving 2,775 patients [189].

Contrary to previous evidence, a multicenter RCT from UK showed that PDD-guided TURBT did not reduce recurrence rates, nor was it cost-effective compared with WL cystoscopy at three years [190] .

*5.12.2 **Narrow-band imaging***

In narrow-band imaging (NBI), the contrast between normal urothelium and hyper-vascular cancer tissue is enhanced. Improved cancer detection has been demonstrated by NBI flexible cystoscopy and NBI-guided biopsies and resection [191-194] (LE: 3b). Two RCTs assessed the reduction of recurrence rates if NBI is used during TURB [194, 195]. Although the overall results were negative, a benefit after three and twelve months was observed for low-risk tumours (pTa LG, < 30 mm, no CIS) [195].

A systematic review and meta-analysis by Russo *et al.*, (17 RCTs and non-RCTs) demonstrated improved detection (diagnostic accuracy) of bladder tumours with either PDD or NBI over WL cystoscopy [196], while another one (including 5,217 patients) showed improved RFS with either enhancement technique [197]. Conversely, a systematic review and network meta-analysis that took into account the use of single post-operative instillation of chemotherapy, concluded that there was a lower likelihood of recurrence at one year only following PDD-guided TURB (with or without single instillation) but not with NBI-guided surgery [198].

5.12.3 IMAGE1 S™, and other technologies

IMAGE1 S™ (formerly named SPIES) is an image enhancement system based on a computerized processing of different colour components that uses specific light filters. Limited evidence has been produced so far in an attempt to validate the 4 different light spectra modalities, suggesting an improvement in the diagnostic accuracy of WL [199, 200]. Early (18 months) follow-up data of an RCT failed to show an advantage in recurrence rate in the IMAGE1 S™ arm over WL, except in a subgroup of primary low intermediate-risk NMIBCs [201].

Confocal laser micro-endoscopy is a high-resolution imaging probe designed to provide endoscopic histological grading in real time but requires further validation [202].

5.13 Second resection (second TURB)

5.13.1 Detection of residual disease and tumour upstaging

The significant risk of residual tumour after initial TURB of TaT1 lesions has been demonstrated [144]. This residual cancer has the potential to worsen oncological outcomes and therefore further emphasises the importance of an effective initial TURB. As patients with an initial incomplete TURB (either from extensive tumour or intra-operative complications) will require a second completion resection, documentation of resection completeness at the time of the initial TURB is essential.

The main purposes of a second TURB are to: (1) clear any residual cancer; (2) re-resect the previous resection site to establish correct pathological staging; and (3) obtain any missing elements of the clinical information (e.g. extent of cancer, involvement of prostatic urethra).

A systematic review analysing data of 8,409 patients with Ta or T1 HG UC demonstrated a 51% risk of persistence and an 8% risk of under-staging in T1 tumours. The analysis also showed a high risk of residual disease in Ta tumours, but this observation was based only on a limited number of cases. Most of the residual lesions were detected at the original tumour location [203].

Another systematic review and meta-analysis of 3,556 patients with T1 tumours showed that the prevalence rate of residual tumours and upstaging to invasive disease after TURB remained high even in a subgroup with detrusor muscle sampled at the initial TURB. In the subgroup of 1,565 T1 tumours with detrusor muscle present, persistent tumour was found in 58% and under-staging occurred in 11% of cases [204].

Prospective trials suggest that post-operative positive urine cytology [205] and Xpert Bladder® (urine mRNA test) [206] are independently associated with residual disease at second resection and risk of future recurrences, respectively. These data, however, need to be confirmed in further studies.

5.13.2 The impact of second resection on treatment outcomes

A second TURB can increase recurrence-free survival (RFS) [207-209], improve outcomes after BCG treatment [210] and provide prognostic information [211-214].

In a retrospective evaluation of a large multi-institutional cohort of 2,451 patients with BCG-treated T1 G3/HG tumours (a second resection was performed in 935 patients), the second resection improved RFS, progression-free survival (PFS) and overall survival (OS) only in patients without detrusor muscle in the initial resection specimen [215]. In a retrospective analysis of 7,666 patients diagnosed with T1 cancer in Ontario, 2,162 underwent a second resection; after adjusting for the effects of confounding variables, only OS (and not CSS) was better in patients who underwent second resection [167]. This apparent improved survival could also be the result of selection bias with fitter patients undergoing second resections. Whilst a single centre retrospective review revealed survival benefit in 209 HGTa patients who underwent a second TURB [216], further evidence is required to identify specific sub-groups of patients with high-grade cancer who are most likely to benefit from a second resection.

5.13.3 Timing of second resection

Retrospective evaluation showed that a second resection performed 14–42 days after initial resection provides longer RFS and PFS compared to second resection performed after 43–90 days [217]. Based on this currently available evidence, a second TURB is recommended in selected cases 2 to 6 weeks after initial resection [217] (for recommendations on patient selection, see Section 5.14).

5.13.4 Recording of results

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

5.14 Pathology report

Pathological investigation of the specimen(s) obtained by TURB and biopsies is an essential step in the decision-making process for BC [218]. Close co-operation between urologists and pathologists is required. Clinical information and high quality of resected and submitted tissue is essential for correct pathological assessment. To obtain all relevant information, the specimen collection, handling and evaluation, should respect the recommendations provided below (see Section 5.14) [219]. In difficult cases, an additional review by an experienced genitourinary pathologist can be considered.

Table 5.1 TURBT checklist*

TURBT checklist - In the Operating Room	
Check the operating room setup	Instruments (sheath, resectoscope, loops, roller if needed, monopolar/ bipolar), camera, video, strainer, specimen container, catheter if needed
Decide irrigation fluid	Saline, Glycine, Water
Disease characteristics checklist	History of bladder cancer, tumour characteristics at cystoscopy if any, imaging results if any, first or second look, visual optimisation planned (PDD/NBI), risk classification
Cystoscopy/ TURBT	
Cystoscopy	Urethra/prostate (males)
	Ureteral orifices
	Diverticula
	Tumour location, number, size, appearance (papillary/sessile), CIS (yes/no)
	White light/PDD/NBI/IMAGE1 S™
	Urine for cytology/bladder wash
TURBT	Resection technique (standard/*en bloc*/cold cup/roller ball cautery)
	Depth of resection
	Complete/incomplete resection
	Prostatic urethra biopsy if performed
	Any additional procedure, i.e. retrograde contrast study
	Estimated blood loss
	Intra-operative complications, if any
	Intravesical therapy if given or planned in recovery setting

**Adapted from Mostafid et al., and Suarez-Ibarrola et al., [140, 220].*
NBI = narrow-band imaging; PDD = photodynamic diagnosis; TURBT = transurethral resection of bladder tumour.

5.15 Summary of evidence and guidelines for transurethral resection of the bladder, biopsies and pathology report

Summary of evidence	**LE**
Transurethral resection of the bladder tumour (TURB) followed by pathology investigation of the obtained specimen(s) is an essential step in the management of NMIBC.	1
The absence of detrusor muscle in the specimen is associated with a significantly higher risk of residual disease and tumour under-staging (with the exception of Ta LG/G1 tumours).	2b
A second TURB can detect residual tumours and tumour under-staging, increase recurrence-free survival, improve outcomes after BCG treatment and provide prognostic information.	2
Photodynamic diagnosis has been shown to improve the detection of bladder cancer, especially CIS.	1a

Recommendations	Strength rating
In patients suspected of having bladder cancer, perform a transurethral resection of the bladder tumour (TURB) followed by pathology investigation of the obtained specimen(s) as a diagnostic procedure and initial treatment step.	Strong
Perform TURB systematically in individual steps: • bimanual palpation under anaesthesia before starting the procedure and at the end; • insertion of the resectoscope, under visual control with inspection of the whole urethra; • inspection of the whole urothelial lining of the bladder; • biopsy from the prostatic urethra (if indicated); • cold-cup bladder biopsies (if indicated); • resection of the tumour; • recording of findings in the surgery report/record including visual impression of grade/stage; • precise description of the specimen(s) for pathology evaluation.	Strong
Performance of individual steps	
Perform *en-bloc* resection or resection in fractions (exophytic part of the tumour, the underlying bladder wall and the edges of the resection area).	Strong
Avoid cauterisation as much as possible during TURB to avoid tissue deterioration.	Strong
Take biopsies from abnormal-looking urothelium.	Strong
Take multiple biopsies (mapping biopsies from the trigone, bladder dome, right, left, anterior and posterior bladder wall) or perform photodynamic diagnosis (PDD) guided biopsies, in case of normal looking urothelium and positive urine cytology.	Strong
Take a sample of the prostatic urethra if there is positive urine cytology without evidence of tumour in the bladder, or if abnormalities of the prostatic urethra are visible (see section 5.11.2).	Strong
Take a sample biopsy of the prostatic urethra in cases of bladder neck tumour, suspicion of bladder CIS and/or T1 disease. If a sample was not taken during the initial procedure, it should be performed at the time of second resection, if the latter is needed (see section 5.11.2).	Weak
Use methods to improve tumour visualisation (fluorescence cystoscopy, narrow-band imaging) during TURB, if available.	Weak
Refer the specimens from different biopsies and resection fractions to the pathologist in separately labelled containers. Submit the tumour base separately especially in large and multifocal tumours or when *en-bloc* resection is not feasible.	Weak
The TURB record must describe tumour location, appearance, size and multifocality, all steps of the procedure, extent, macroscopic completeness of resection as well as any complications.	Strong
In patients with positive cytology, but negative cystoscopy, exclude an upper tract urothelial carcinoma, CIS in the bladder (by mapping biopsies or PDD-guided biopsies) and tumour in the prostatic urethra (by prostatic urethra biopsy).	Strong
Perform a second TURB in the following situations: • after incomplete initial TURB, or in case of doubt about completeness of a TURB; • if there is no detrusor muscle in the specimen after initial resection, with the exception of Ta LG/G1 tumours and primary CIS; • in T1 tumours.	Strong
If indicated, perform a second TURB within 2–6 weeks after the initial resection. This second TURB should include resection of the primary tumour site.	Weak
Record the pathology results of the second TURB as it reflects the quality of the initial resection.	Weak
Inform the pathologist of prior treatments (intravesical therapy, radiotherapy, etc.).	Strong
The pathological report should specify tumour location, tumour grade and stage, lymphovascular invasion, subtypes of urothelial carcinoma, presence of CIS and detrusor muscle.	Strong

6. PREDICTING DISEASE RECURRENCE AND PROGRESSION

6.1 TaT1 tumours

Treatment should take into account a patient's prognosis. In order to predict the risk of disease recurrence and/or progression, several prognostic models for specified patient populations have been introduced.

*6.1.1 **Scoring models using the WHO 1973 classification system***

6.1.1.1 The 2006 European Organisation for Research and Treatment of Cancer (EORTC) scoring model

To be able to predict both the short- and long-term risks of disease recurrence and progression in individual patients, the EORTC Genito-Urinary Cancer Group (GUCG) published a scoring system and risk tables based on the WHO 1973 classification in 2006 [221]. The scoring system is based on the 6 most significant clinical and pathological factors in patients mainly treated by intravesical chemotherapy:

- number of tumours;
- tumour diameter;
- prior recurrence rate;
- T category;
- concurrent CIS;
- WHO 1973 tumour grade.

Using the 2006 EORTC scoring model, individual probabilities of recurrence and progression at 1 and 5 years may be calculated (https://www.omnicalculator.com/health/eortc-bladder-cancer).

6.1.1.2 The model for patients with Ta G1/G2 (WHO 1973) tumours treated with chemotherapy

Patients with Ta G1/G2 tumours receiving chemotherapy were stratified into 3 risk groups for recurrence, taking into account the history of recurrences, history of intravesical treatment, tumour grade (WHO 1973), number of tumours and adjuvant chemotherapy [222].

6.1.1.3 Club Urologico Español de Tratamiento Oncologico (CUETO) scoring model for BCG-treated patients

A model that predicts the risk of recurrence and progression, based on 12 doses of intravesical BCG over a 5 to 6 months period following TURB, has been published by the CUETO (Spanish Urological Oncology Group). It is based on an analysis of 1,062 patients from 4 CUETO trials that compared different intravesical BCG treatments. No immediate post-operative instillation or second TURB was performed in these patients. The scoring system is based on the evaluation of seven prognostic factors:

- gender;
- age;
- prior recurrence status;
- number of tumours;
- T category;
- associated CIS;
- WHO 1973 tumour grade.

Using this model, the calculated risk of recurrence is lower than that obtained by the EORTC tables. For progression, probability is lower only in high-risk patients [223] (LE: 2a). The lower risks in the CUETO tables may be attributed to the use of BCG in this study. The prognostic value of the EORTC scoring system has been confirmed by data from the CUETO patients treated with BCG [224] and by long-term follow-up in another patient population [225].

6.1.1.4 The 2016 EORTC scoring model for patients treated with maintenance BCG

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 WHO 1973 grade for disease progression and disease- specific survival, while age and WHO 1973 grade were the most important prognostic factors for OS. T1 G3 patients did poorly, with 1- and 5-year disease-progression rates of 11.4% and 19.8%, respectively. Using these data, EORTC risk groups and nomograms for BCG-treated patients were developed [226].

*6.1.2 **Scoring model using the WHO 2004/2016 and WHO 1973 classification systems***

6.1.2.1 EAU NMIBC 2021 scoring model

To update the risk of disease progression and create new prognostic factor risk groups using both the WHO 1973 and WHO 2004/2016 classification systems (without central pathology review), individual patient data from 3,401 primary patients treated from 1990 to 2018 were used [227] (see Section 4.5). Only patients treated with TURB ± intravesical chemotherapy were included, those treated with adjuvant intravesical BCG were excluded because BCG may reduce the risk of disease progression. From the multivariate analyses, tumour stage, WHO 1973 grade, WHO 2004/2022 grade, concomitant CIS, number of tumours, tumour size and age were independent predictors of disease progression [227].

This is the only available model where the WHO 2004/2022 classification system is included as one of the parameters to calculate an individual patient's risk group and probability of progression. As the WHO 2004/2022 classification system is the main grading classification system used by pathologists, the Guidelines Panel recommends to use the 2021 EAU NMIBC scoring model for risk groups definition (see Section 6.3).

The 2021 EAU NMIBC scoring model determines the risk of tumour progression, but not recurrence; therefore any of the models mentioned in Section 6.1.1 may be used for calculation of an individual's risk of disease recurrence.

*6.1.3 **Further prognostic factors***

Further prognostic factors have been described in selected patient populations:

- In T1 HG/G3 tumours, important prognostic factors were female sex, CIS in the prostatic urethra in men treated with an induction course of BCG, and age, tumour size and concurrent CIS in BCG-treated patients (62% with an induction course only) [177, 228].
- Attention must be given to patients with T1 HG/G3 tumours in bladder diverticulum because of the absence of muscle layer in the diverticular wall [229].
- In patients with T1 tumours, the finding of residual T1 disease at second TURB is an unfavourable prognostic factor [212-214].
- In patients with T1G2 tumours treated with TURB, recurrence at 3 months was the most important predictor of progression [230].
- 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 [225, 231].

6.2 Primary carcinoma *in situ*

Without any treatment, approximately 54% of patients with CIS progress to muscle-invasive disease [232] (LE: 3). There are no reliable prognostic factors, but some studies, however, have reported a worse prognosis in concurrent CIS and T1 tumours compared to primary CIS [233, 234], in extended CIS [235] and in CIS in the prostatic urethra [177]. The response to intravesical treatment with BCG or chemotherapy is an important prognostic factor for subsequent progression and death caused by BC [223, 224, 230]. Approximately 10 to 20% of complete responders eventually experience disease progression to muscle-invasive disease, compared with 66% of non- responders [236, 237].

6.3 Patient stratification into risk groups

To be able to facilitate treatment recommendations, the Guidelines Panel recommends the stratification of patients into risk groups based on their probability of progression to muscle-invasive disease. The new risk group definitions provided in these EAU Guidelines are based on an individual patient data analysis in primary patients and the calculation of their progression scores (2021 EAU NMIBC scoring model) as presented in Sections 4.5 and 6.1.2) [227].

For calculation of the risk group in individual patients, either one, or both, of the WHO 1973 and WHO 2004/2016 classification systems may be used. The probability of progression at 5 years varies from less than 1% to more than 40% between the risk groups.

For factors where individual patient data were not collected such as subtypes of UC, LVI, primary CIS and CIS in the prostatic urethra; literature data have been used to classify patients into risk groups.

The clinical compositions of the new EAU NMIBC prognostic factor risk groups based on the WHO 2004/2016 or WHO 1973 classification systems are provided in Table 6.1. Applications for the web (www.nmibc.net), iOS and Android have been developed to facilitate determining a patient's risk group in daily clinical practice. The individual probability of disease progression at 1, 5 and 10 years for the new EAU NMIBC risk groups is presented in Table 6.2. A single-centre study validated the EAU NMIBC 2021 scoring model in 529 patients who

received BCG [238]. The authors found that the progression risk for the EAU 2021 high- and very high-risk groups were significantly lower in BCG-treated patients than that in Table 6.2 [227]. These lower risks may be attributed to the use of BCG.

Table 6.1: Clinical composition of the new EAU NMIBC prognostic factor risk groups based on the WHO 2004/2016 or the WHO 1973 grading classification systems [227]

- Only one of the two classification systems (WHO 1973 or WHO 2004/2016) is required to use this table.
- If both classification systems are available in an individual patient, the Panel recommends using the risk group calculation based on the WHO 1973 as it has better prognostic value.
- The category of LG tumours (WHO 2004/2016) also includes patients with tumours classified as PUNLMP.
- Additional clinical risk factors are: age > 70; multiple papillary tumours; and tumour diameter > 3 cm.

Risk group	
Low Risk	• A primary, single, TaT1 LG/G1 tumour < 3 cm in diameter without CIS in a patient ≤ 70 years • A primary Ta LG/G1 tumour without CIS with at most ONE of the additional clinical risk factors
Intermediate Risk	• Patients without CIS who are not included in either the low-, high-, or very high-risk groups
High Risk	• All T1 HG/G3 without CIS, EXCEPT those included in the very high-risk group • All CIS patients, EXCEPT those included in the very high-risk group
	Stage, grade with additional clinical risk factors: • Ta LG/G2 or T1G1, no CIS with all 3 risk factors • Ta HG/G3 or T1 LG, no CIS with at least 2 risk factors • T1G2 no CIS with at least 1 risk factor
Very High Risk	**Stage, grade with additional clinical risk factors:** • Ta HG/G3 and CIS with all 3 risk factors • T1G2 and CIS with at least 2 risk factors • T1 HG/G3 and CIS with at least 1 risk factor • T1 HG/G3 no CIS with all 3 risk factors

The scoring model is based on individual patient data, but does not consider patients with primary CIS (high risk) or with recurrent tumours, as well as some pathologic parameters like subtypes of UC (see Section 4.7) and LVI. Nevertheless:

- Based on data from the literature, all patients with CIS in the prostatic urethra, with subtypes of UC (see Section 4.8) or with LVI should be included in the very high-risk group.
- Patients with recurrent tumours should be included in the intermediate-, high-, or very high-risk groups according to their other prognostic factors.

Table 6.2: Probabilities of disease progression in 1, 5 and 10 year(s) for the new EAU NMIBC risk groups [227]*

Risk group	*Probability of Progression and 95% Confidence Interval (CI)*		
	1 Year	5 Years	10 Years
New Risk Groups with WHO 2004/2016			
Low	0.06% (CI: 0.01%–0.43%)	0.93% (CI: 0.49%–1.7%)	3.7% (CI: 2.3%–5.9%)
Intermediate	1.0% (CI: 0.50%–2.0%)	4.9% (CI: 3.4%–7.0%)	8.5% (CI: 5.6%–13%)
High	3.5% (CI: 2.4%–5.2%)	9.6% (CI: 7.4%–12%)	14% (CI: 11%–18%)
Very High	16% (CI: 10%–26%)	40% (CI: 29%–54%)	53% (CI: 36%–73%)
New Risk Groups with WHO 1973			
Low	0.12% (CI: 0.02%–0.82%)	0.57% (CI: 0.21%–1.5%)	3.0% (CI: 1.5%–6.3%)
Intermediate	0.65% (CI: 0.36%–1.2%)	3.6% (CI: 2.7%–4.9%)	7.4% (CI: 5.5%–10%)
High	3.8% (CI: 2.6%–5.7%)	11% (CI: 8.1%–14%)	14% (CI: 10%–19%)
Very High	20% (CI: 12%–32%)	44% (CI: 30%–61%)	59% (CI: 39%–79%)

WHO = World Health Organization.

**Table 6.2 does not include patients with subtypes of urothelial carcinoma (variant histologies), LVI, CIS in the prostatic urethra, primary CIS or recurrent patients.*

**Please note that these percentages refer to patients who were not (immediately) treated with adjuvant BCG instillations after their primary TUR.*

6.4 Summary of evidence and guidelines for stratification of non-muscle-invasive bladder cancer

Summary of evidence	LE
The EAU NMIBC 2021 scoring model and risk tables predict the short- and long-term risks of disease progression in individual patients with primary NMIBC using either the WHO 1973 or the WHO 2022 classification system (see Section 6.1.2.1).	2b
The 2006 EORTC scoring model and risk tables predict the short- and long-term risks of disease recurrence and progression in individual patients with NMIBC using the WHO 1973 classification system (see Section 6.1.1.1).	1b
Patients with Ta G1/G2 tumours receiving chemotherapy have been further stratified into 3 risk groups for recurrence, taking into account the history of recurrences, history of intravesical treatment, tumour grade (WHO 1973), number of tumours and adjuvant chemotherapy (see Section 6.1.1.2).	2b
In patients treated with 5 to 6 months of BCG, the CUETO scoring model predicts the short- and long-term risks of disease recurrence and progression using the WHO 1973 classification system (see Section 6.1.1.3).	1b
In patients receiving at least 1 year of BCG maintenance; prior recurrence rate and number of tumours are the most important prognostic factors for disease recurrence. Stage and grade are the most important prognostic factors for disease progression and disease-specific survival; patient age and grade (WHO 1973) are the most important prognostic factors for OS (see Section 6.1.1.4).	1b

Recommendations	Strength rating
Stratify patients into 4 risk groups to predict progression, according to Table 6.1. A patient's risk group can be determined using the 2021 EAU risk group calculator available at www.nmibc.net.	Strong
For information about the risk of disease progression in a patient with primary TaT1 tumours, not treated with bacillus Calmette-Guérin (BCG), use the data from Table 6.2.	Strong
Use the 2006 EORTC scoring model to predict the risk of tumour recurrence in individual patients not treated with BCG.	Strong
Use the 2016 EORTC scoring model or the CUETO risk scoring model to predict the risk of tumour recurrence in individual patients treated with BCG intravesical immunotherapy (the 2016 EORTC model is calculated for 1 to 3 years of maintenance, the CUETO model for 5 to 6 months).	Strong

7. DISEASE MANAGEMENT

7.1 Counselling of smoking cessation

It has been confirmed that smoking increases the risk of tumour recurrence and progression in NMIBC patients [239-241] as well as mortality in all BC patients [242]. A subgroup analysis of 4,405 patients in a large systematic review revealed that current smokers had a significantly higher risk of recurrence compared with former smokers [241]. Patients should be counselled to stop smoking due to the general health risks associated with tobacco smoking [229, 243-245].

7.2 Office-based fulguration and laser vaporisation

In patients with a history of small Ta LG/G1 tumours, fulguration, or laser vaporisation of small papillary recurrences on an outpatient basis can reduce the therapeutic burden [246, 247]. In a prospective RCT, laser photocoagulation with intravesical lidocaine in an outpatient setting proved non inferior to standard TURB under general anaesthesia for the 4 months recurrence rate. Notably, the laser fulguration procedure resulted in only a modest pain score (2.4) and was preferred by 98% of patients [248].

7.3 Active Surveillance

With recurrence in LG(G1) Ta tumours being more likely low grade and non-invasive [249-251] the risk of progression to a higher grade or stage is infrequent to rare [252-254]. Expectant management or active surveillance (AS), offer an alternative to TURB and office-based fulguration. Observing no progression to MIBC, Soloway *et al.*, first recommended this approach in 2003 [255] and Miyake *et al.*, subsequently proposed an algorithm for AS using changes in size and multifocality as triggers for intervention [256]. However, from a review undertaken by the EAU Young Academic Urology group [257], it appears that the level of evidence in favour of AS is low, with observational studies having heterogenous selection criteria, triggers for intervention and surveillance tools. The multicentre prospective Bladder Cancer Italian Active Surveillance (BIAS) project, conversely, demonstrated that AS is feasible in selected patients [258, 259] and its success be predicted by prognostic variables associated to TaLG disease [260]. However, additional evidence from quality clinical trials is required.

7.4 Adjuvant intravesical treatment

Although TURB by itself can eradicate a TaT1 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 [144]. It is therefore necessary to consider adjuvant therapy in all patients.

*7.4.1 **Post-operative irrigation***

Two systematic reviews [261, 262] and one meta-analysis [263] suggest efficacy of continuous irrigation in the prevention of early recurrences. In case intravesical chemotherapy is not feasible, irrigation of the bladder might be considered. Optimal volume infused and duration of irrigation remains unknown.

*7.4.2 **Intravesical chemotherapy***

7.4.2.1 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 on residual tumour cells at the resection site and on small overlooked tumours [264-267]. 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 [268-271]. In a systematic review and individual patient data meta-analysis of 2,278 eligible patients [268], SI reduced the 5-year recurrence rate by 14%, from 59% to 45%. Only patients with primary tumours or intermediate-risk recurrent tumours with a prior recurrence rate of < 1 recurrence/year and those with a 2006 EORTC recurrence score < 5 benefited from SI. In patients with a 2006 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. No randomised comparisons of individual drugs have been conducted [268-271].

Single instillation with mitomycin C (MMC), epirubicin or pirarubicin [268], as well as gemcitabine [271], have all shown to lower the intravesical recurrence rate. Single instillation with gemcitabine was superior to saline in a RCT with approximately 200 patients per arm with remarkably low toxicity rates [272]. These findings are in contrast with a previous study, which, however, used a shorter instillation time [273]. In the Böhle *et al.*, study, continuous saline irrigation was used for 24 hours post-operatively in both arms, which could explain the low recurrence rate in the control arm [273].

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 the extracellular matrix [264, 274-276]. In all SI studies, the instillation was administered within 24 hours. Two RCTs found no overall impact of SI with apaziquone, a bio reductive prodrug similar to MMC; in contrast, a *post-hoc* analysis did find a reduction of recurrence risk in patients receiving apaziquone within 90 minutes following TURB [277].

To maximise the efficacy of SI, one should devise flexible practices that allow the instillation to be given as soon as possible after TURB, preferably within the first two hours in the recovery room or even in the operating theatre. As severe complications have been reported in patients with drug extravasation, safety measures should be maintained (see Section 7.7) [278, 279]. To allow for optimal compliance with this Level 1 evidence, clinical teams are encouraged to explore barriers and facilitators within their practice [280].

7.4.2.2 Additional adjuvant intravesical chemotherapy instillations

The need for further adjuvant intravesical therapy depends on prognosis. In low-risk patients (Tables 6.1 and 6.2), a SI reduces the risk of recurrence and is considered to be the standard and complete treatment [268, 269]. For other patients, however, a SI remains an incomplete treatment because of the considerable likelihood of recurrence and/or progression (Tables 6.1 and 6.2). Efficacy data for the following comparisons of application schemes were published.

Single installation only vs. SI and further repeat instillations

In one study, further chemotherapy instillations after SI improved RFS in intermediate-risk patients [281].

Repeat chemotherapy instillations vs. no adjuvant treatment

A large meta-analysis of 3,703 patients from 11 RCTs showed a highly significant (44%) reduction in the odds of recurrence at one year in favour of chemotherapy over TURB alone [282]. This corresponds to an absolute difference of 13–14% in the proportion of patients with recurrence. Contrary to these findings, two meta-analyses have demonstrated that BCG therapy may also reduce the risk of tumour progression [283, 284] (see Section 7.2.2.1). Moreover, BCG maintenance therapy appears to be significantly better in preventing recurrences than chemotherapy [285-287] (see Section 7.2.2.1). However, BCG causes significantly more side effects than chemotherapy [287].

Single instillation + further repeat instillations vs. later repeat instillations only

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 [288-291]. A RCT including 2,243 NMIBC patients, which compared SI of MMC with an instillation of MMC delayed two weeks after TURB (followed by further repeat instillations in both treatment arms), showed a significant reduction of 9% in the risk of recurrence at 3 years in favour of SI, from 36% to 27%. The effect was significant in the intermediate- and high-risk groups of patients receiving additional adjuvant MMC instillations [288]. Since the author's definition of the risk groups differed significantly in the initial publication, they adapted their patient stratification in the second analysis and consistently showed improved efficacy of SI followed by repeat MMC instillations [292]. The results of this study should be considered with caution since some patients did not receive adequate therapy. Another RCT found no impact of SI with epirubicin followed by further chemotherapy or BCG instillations in a cohort of predominant HR BC patients [293].

The optimal schedule of intravesical chemotherapy instillations

The length and frequency of repeat chemotherapy instillations is still controversial; however, it should not exceed one year [291]. A systematic review of 16 comparative studies concluded that most of the available evidence does not support the use of maintenance chemotherapy over induction only in the treatment of NMIBC [294].

7.4.2.3 Measures to improve the efficacy of intravesical chemotherapy

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

Two prospective RCTs showed that optimized intravesical administration of MMC reduced recurrence rates, either by a combination of measures (higher MMC-dose, peroral sodium bicarbonate, and refraining from drinking) [295] and by adding cytosine arabinoside [296], respectively. The value of these measures in addition to alternative maintenance schedules is not known however MMC admixtures ≥ 1 mg/ml do not achieve full solubilisation which might lead to decreased drug exposure to the bladder [297]. Another trial reported that duration of a one- hour instillation of MMC was more effective compared to a 30-minute instillation, but no efficacy comparisons are available for one- vs. two-hour durations of instillation [298]. Another RCT using epirubicin has documented that concentration is more important than treatment duration [299]. In view of these data, instructions are provided (see Section 7.7).

7.4.2.3.2 Device-assisted intravesical chemotherapy

Hyperthermic intravesical chemotherapy

Different technologies which increase the temperature of instilled MMC are available. A recent systematic review and meta-analysis including four RCTs suggests similar toxicity as for BCG with maintenance schedule [300].

Microwave-induced hyperthermia effect (RITE)

Promising data have been presented on enhancing the efficacy of MMC using microwave-induced hyperthermia in patients with high-risk tumours [301]. In one RCT comparing one year of BCG with one year MMC and microwave-induced hyperthermia in patients with intermediate- and high-risk BC, increased RFS at 24 months in the MMC group was demonstrated [302].

Conductive chemohyperthermia

In an open-label phase II RCT including 259 patients, HIVEC chemo-hyperthermia failed to demonstrate an improvement in DFS at 24 months over standard adjuvant intravesical chemotherapy in intermediate-risk NMIBC (61% vs. 60%), with a higher risk of treatment discontinuation (59% vs. 89% of completed planned treatments) [303]. These results are in line with the multicentre HIVEC 1 phase 3 open label RCT, including 212 intermediate-risk patients, showing that four-month adjuvant hyperthermic MMC using the COMBAT system in intermediate-risk NMIBC was well tolerated, but was not superior to normothermic MMC at 24 months [304].

In a pilot phase II RCT on 50 high-risk NMIBCs, HIVEC™ MMC showed early outcomes comparable to BCG (24 months RFS, 86.5% with HIVEC™ and 71.8% with BCG, p = 0.184) [305]. These data need to be corroborated by further studies.

Electromotive drug administration

The efficacy of MMC using electromotive drug administration (EMDA) sequentially combined with BCG in patients with high-risk tumours has been demonstrated in one small RCT [306]. The definitive conclusion, however, needs further confirmation. For application of device-assisted instillations in patients recurring after BCG treatment, see Section 7.9.3.

7.4.2.4 Summary of evidence - intravesical chemotherapy

Summary of evidence	**LE**
In patients with low-risk NMIBC and in those with a small Ta LG/G1 recurrence detected more than one year after previous TURB, a SI significantly reduces the recurrence rate compared to TURB alone.	1a
Single instillation might have an impact on recurrence even when further adjuvant chemotherapy instillations are given, but not in high-risk NMIBC treated with adjuvant BCG.	3
Repeat chemotherapy instillations (with or without previous SI) improve RFS in intermediate-risk patients.	2a

7.4.3 ***Intravesical bacillus Calmette-Guérin (BCG) immunotherapy***

7.4.3.1 Efficacy of BCG

7.4.3.1.1 Recurrence rate

Five meta-analyses have confirmed that BCG after TURB is superior to TURB alone or TURB plus chemotherapy for preventing the recurrence of NMIBC [285, 307-310]. Three RCTs of intermediate- and high-risk tumours have compared BCG with epirubicin and interferon (INF) [311], MMC [312], or epirubicin alone [286] and have confirmed the superiority of BCG for prevention of tumour recurrence (LE: 1a). The effect is long lasting [286, 312] and was also observed in a separate analysis of patients with intermediate-risk tumours [286]. One meta-analysis [285] has evaluated the individual data from 2,820 patients enrolled in 9 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. A Cochrane systematic review confirmed that BCG is more effective in reducing the recurrence rate over MMC [313].

7.4.3.1.2 Progression rate

Two meta-analyses have demonstrated that BCG therapy delays and potentially lowers the risk of tumour progression [283, 284, 310] (LE: 1a). A meta-analysis carried out by the EORTC GUCG has evaluated data from 4,863 patients enrolled in 24 RCTs. In 20 of the trials, some form of BCG maintenance was used. Based on a median follow-up of 2.5 years, tumours progressed in 9.8% of the patients treated with BCG compared to 13.8%

in the control groups (TURB alone, TURB and intravesical chemotherapy, or TURB with the addition of other immunotherapy). This shows a reduction of 27% in the odds of progression with BCG maintenance treatment. The size of the reduction was similar in patients with TaT1 papillary tumours and in those with CIS [284]. A RCT with long-term follow-up has demonstrated significantly fewer distant metastases and better overall- and disease-specific survival in patients treated with BCG compared to epirubicin [286] (LE: 1b). In contrast, an individual patient data meta-analysis and Cochrane review were not able to confirm any statistically significant difference between MMC and BCG for progression, survival, and cause of death [285, 313].

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 a BCG maintenance schedule was applied.

7.4.3.1.3 Influence of further factors

Two other meta-analyses have suggested a possible bias in favour of BCG arising from the inclusion of patients previously treated with intravesical chemotherapy [314]. In the individual patient data meta-analysis, however, BCG maintenance was more effective than MMC in reduction of recurrence rate, both in patients previously treated and not previously treated with chemotherapy [285] (LE: 1a). It was demonstrated that BCG was less effective in patients > 70 years of age, but still more effective than epirubicin in a cohort of elderly patients [315] (LE: 1a). According to a cohort analysis, the risk of tumour recurrence after BCG was shown to be higher in patients with a previous history of UTUC [316].

7.4.3.2 BCG strain

Although smaller studies without maintenance demonstrated some differences between strains [316-318], a network meta-analysis identified ten different BCG strains used for intravesical treatment in the published literature but was not able to confirm superiority of any BCG strain over another [319].

Similarly, a meta-analysis of prospective RCTs [284], published data from a prospective registry [320] as well as from a *post-hoc* analysis of a large phase II prospective trial assessing BCG and INF-α in both BCG-naive and BCG-failure patients did not suggest any clear difference in efficacy between the different BCG strains [321]. The quality of data, however, does not allow definitive conclusions.

7.4.3.3 BCG toxicity

Bacillus Calmette-Guérin intravesical treatment is associated with more side effects compared to intravesical chemotherapy [284, 313]. However, serious side effects are encountered in < 5% of patients and can be treated effectively in almost all cases [322]. The incidence of BCG infections after BCG instillations was 1% in a registry-based cohort analysis [323]. It has been shown that a maintenance schedule is not associated with an increased risk of side effects compared to an induction course [322]. Side effects requiring treatment stoppage were seen more often in the first year of therapy [324]. Elderly patients do not seem to experience more side effects leading to treatment discontinuation [325]. No significant difference in toxicity between different BCG strains was demonstrated [320]. Symptoms may be the result of side effects of the BCG treatment or caused by bladder disease (widespread CIS) itself. Consequently, the burden of symptoms is reduced after completion of the treatment in a significant number of patients albeit delayed hypersensitivity to BCG may rarely present even years after completion of treatment [326].

Major complications can appear after systemic absorption of the drug. Thus, contraindications of BCG intravesical instillation should be respected (see Section 7.9). The presence of leukocyturia, nonvisible haematuria or asymptomatic bacteriuria is not a contraindication for BCG application, and antibiotic prophylaxis is not necessary in these cases [131, 327] (LE: 3). Three RCTs showed reduced side effects by administering different quinolones in conjunction with the BCG-instillations [328-330]. The latter, by using two doses of levofloxacin (at 6 and 12 hours after first voiding) in conjunction with each BCG-instillation, reduced the proportion of patients with high-grade side effects, both local (pollakisuria) and systemic (fever), without improving the completion rate of the maintenance regimen or the risk of severe BCG related adverse events [330].

Bacillus Calmette-Guérin should be used with caution in immunocompromised patients. Immunosuppression, for example human immunodeficiency virus (HIV) infection, poses relative contraindications [331], 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 [332-334]. Kidney transplant recipients can be safely treated with BCG [335].

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 [336, 337] (Table 7.1).

Table 7.1: Management options for side effects associated with intravesical BCG [337-340]

Management options for local side effects (modified from International Bladder Cancer Group)	
Symptoms of cystitis	Phenazopyridine, propantheline bromide, or non-steroidal anti-inflammatory drugs (NSAIDs).
	If symptoms improve within a few days: continue instillations.
	If symptoms persist or worsen: a. Postpone the instillation. b. Perform a urine culture. c. Start empirical antibiotic treatment.
	If symptoms persist even with antibiotic treatment: a. With positive culture: adjust antibiotic treatment according to sensitivity. b. With negative culture: quinolones* and potentially analgesic anti-inflammatory instillations once daily for 5 days (repeat cycle if necessary) [338].
	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 [339]	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.
	Reactive arthritis: NSAIDs.
	If no/partial response, proceed to corticosteroids, high-dose quinolones or antituberculosis drugs [340].
Persistent high-grade fever (> 38.5°C for > 48 h)	Permanent discontinuation of BCG instillations.
	Immediate evaluation: urine culture, blood tests, chest X-ray.
	Prompt treatment with more than two antimicrobial agents while diagnostic evaluation is conducted.
	Consultation with an infectious diseases specialist.
BCG sepsis	Prevention: initiate BCG at least 2 weeks post-transurethral resection of the bladder (if no signs and symptoms of haematuria).
	Cessation of BCG.
	For severe infection: • 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.

** Persistent severe cystitis symptoms associated with BCG use have a high risk to underlie a complicated UTI (even in the absence of a positive culture) and thus no restriction applies to the empirical use of quinolones by the Pharmacovigilance Risk Assessment Committee of the EMA (see also Section 3.7 Complicated UTI and 3.7.4.1- Choice of antimicrobials of the EAU Guidelines on Urological Infection 2022) [341, 342].*

7.4.3.4 Optimal BCG schedule

Induction BCG instillations are given according to the empirical 6-weekly schedule introduced by Morales *et al.*, [343]. For optimal efficacy, BCG must be given in a maintenance schedule [283-285, 310]. Many different maintenance schedules have been used, ranging from a total of 10 instillations given in 18 to 27 weeks over 3 years [344]. The optimal 3-years maintenance schedule is outlined in recommendation table 7.10.

7.4.3.4.1 Optimal number of induction instillations and frequency of instillations during maintenance

The optimal number of induction instillations and frequency of maintenance instillations were evaluated by NIMBUS, a prospective phase III RCT. Safety analysis after 345 randomised patients demonstrated that a reduced number of instillations (3 instillations in induction and 2 instillations at 3, 6 and 12 months) proved inferior to the standard schedule (6 instillation in induction and 3 instillations at 3, 6 and 12 months) regarding the time to first recurrence [345]. In a RCT including 397 patients CUETO showed that in high-risk tumours a maintenance schedule with only one instillation every 3 months for 3 years was not superior to induction therapy only, which suggested that one instillation may be suboptimal to 3 instillations in each maintenance cycle [346].

7.4.3.4.2 Optimal length of maintenance

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 [283].

In a RCT of 1,355 patients, the EORTC has shown that when BCG is given at full dose, 3 years' maintenance (3-weekly instillations 3, 6, 12, 18, 24, 30 and 36 months) reduces the recurrence rate compared to one year in high- but not in intermediate-risk patients. There were no differences in progression or OS. In the 3-year arm, however, 36.1% of patients did not complete the 3-year schedule [347]. The main reason why these patients stopped treatment was treatment inefficacy, not toxicity.

7.4.3.5 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 [348, 349]. 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 [350]. 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 [324, 347]. In a recent meta-analysis of 9 RCTs, patients who received less than half of the standard BCG dose experienced less adverse events as compared to patients receiving the full dose, but faced more unfavourable outcomes such as higher rates of disease recurrences [351].

7.4.3.6 BCG shortage

A statement by the Panel on BCG shortage can be accessed online:
https://uroweb.org/guidelines/non-muscle-invasive-bladder-cancer/publications-appendices.

7.4.3.7 Summary of evidence - BCG treatment

Summary of evidence	**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 and intravesical chemotherapy.	1a
For optimal efficacy, BCG must be given in a maintenance schedule. A complete BCG schedule comprises an induction phase of 6-weekly instillations, followed by a maintenance phase of three-weekly instillations at 3, 6, 12, 18, 24, 30 and 36 months, respectively.	1a
Three-year maintenance is more effective than one year to prevent recurrence in patients with high-risk tumours, but not in patients with intermediate-risk tumours.	1a

*7.4.4 **Combination therapy***

7.4.4.1 Intravesical BCG plus chemotherapy versus BCG alone

In one RCT, a combination of MMC and BCG was shown to be more effective in reducing the risk of disease recurrence while increasing toxicity compared to BCG monotherapy. Using similar BCG schedules in both groups, each BCG instillation in the combination group was preceded a day before by an added MMC instillation [352]. In a 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 [306, 353]. Two meta-analyses demonstrated improved disease-free survival (DFS), but no benefit in PFS in patients treated with combination treatment comparing to BCG monotherapy [353, 354].

7.4.4.2 Combination treatment using interferon

In a Cochrane meta-analysis of 4 RCTs, a combination of BCG and IFN-2α did not show a clear difference in recurrence and progression over BCG alone [355]. In one study, weekly MMC followed by monthly BCG alternating with IFN-2α showed a higher probability of recurrence compared to MMC followed by BCG alone [356]. Additionally, a RCT in a similar population of NMIBC comparing BCG monotherapy with a combination of epirubicin and INF for up to two years showed the latter was significantly inferior to BCG monotherapy in preventing recurrence [357].

7.4.4.3 Sequential chemotherapy instillations

Preclinical data suggest that the efficacy of intravesical chemotherapy instillations can be improved by combinations compared to the administration of single agents only [358]. Sequential (immediate) instillations of gemcitabine and docetaxel was initially reported in 2015 in the wake of BCG-shortage but also at times of limited access to mitomycin [359]. Subsequently other sequential chemotherapy combinations such as valrubicin and docetaxel have been suggested [360]. Over time, additional retrospective data have accumulated where sequential gemcitabine and docetaxel instillations were used in patients recurring after induction BCG and BCG-unresponsive disease [361]; in patients with recurrence after BCG-induction but not fulfilling the criteria for BCG-unresponsive disease [362]; and also in BCG-naïve high-risk patients [363]. Thus, in patients with BCG-unresponsive disease when the treatment standard (radical cystectomy) is not feasible due to age and/or comorbidity or when patients are unwilling to accept radical surgery, sequential instillations with gemcitabine and docetaxel is an emerging treatment concept awaiting further prospective scientific evaluation.

*7.4.5 **Specific aspects of treatment of carcinoma in situ***

7.4.5.1 Treatment strategy

The detection of concurrent CIS increases the risk of recurrence and progression of TaT1 tumours [221, 223]. In this case further treatment according to the criteria summarised in Sections 7.4.2, 7.4.3 and 7.9 is mandatory. Carcinoma *in situ* cannot be cured by an endoscopic procedure alone. Histological diagnosis of CIS must be followed by further treatment, either intravesical BCG instillations or RC. Tumour-specific survival rates after immediate RC for CIS are excellent, but a large proportion of patients might be over-treated [232].

7.4.5.2 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 [232-235, 356]. Up to 50% of complete responders might eventually show recurrence with a risk of invasion and/or extravesical recurrence [235, 276, 344, 364].

7.4.5.3 Prospective randomised trials on intravesical BCG or chemotherapy

Unfortunately, there have been few RCTs in patients with CIS only. A meta-analysis of clinical trials comparing intravesical BCG to intravesical chemotherapy in patients with CIS has shown a significantly increased response rate after BCG and a reduction of 59% in the odds of treatment failure with BCG [365].

In an EORTC-GUCG meta-analysis of tumour progression, in a subgroup of 403 patients with CIS, BCG reduced the risk of progression by 35% as compared to intravesical chemotherapy or immunotherapy [284]. The combination of BCG and MMC was not superior to BCG alone [366]. 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.

7.4.5.4 Treatment of CIS in the 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 [367]. Patients with extravesical involvement had worse survival than those with bladder CIS alone [367]. In the prostate, CIS might be present only in the epithelial lining of the prostatic urethra or in the prostatic ducts [368]. 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 [137, 369]. However, potential spread of CIS has to be considered; no suprapubic trocar-placed catheter should be used.

In patients with prostatic duct involvement there are promising results of BCG, but only from small series. The data are insufficient to provide clear treatment recommendations and radical surgery should be considered [369, 370].

7.4.5.5 Summary of evidence - treatment of carcinoma in situ

Summary of evidence	**LE**
Carcinoma *in situ* cannot be cured by an endoscopic procedure alone.	4
Compared to intravesical chemotherapy, intravesical BCG maintenance instillations increase the complete response rate, the overall percentage of patients who remain disease free, and reduce the risk of tumour progression.	1b

7.5 Intravesical chemoablation and neoadjuvant treatment

Two different modalities of administering chemotherapy as first-line approach for a presumed NMIBC have been reported: neoadjuvant intravesical chemotherapy before TURB or chemoresection of the tumour as a replacement of TURB.

Neoadjuvant

Hypothesis-generating findings from an older RCT comparing immediate pre-operative device-assisted (EMDA) MMC with post-operative SI with MMC and TURB only, showed improved long-term RFS among patients treated prior to TURB [371], and thus even suggest a long-term effect after neoadjuvant instillations. While this has not been reproduced by other groups, two recent small neoadjuvant RCTs have reported conflicting results on the ability of neoadjuvant administration of MMC to improve outcomes over the standard approach [372, 373].

Chemoablation

Older marker lesion studies have shown that chemoablation with a single intravesical chemotherapy instillation can achieve a complete response in a proportion of patients [374]; therefore, making it possible to avoid TURB. In recurrent low-grade [375] and recurrent Ta tumours [376], 4 and 6 intravesical MMC instillations achieved complete response in 37% and 57% of the patients, respectively. In an update of the DaBlaCa-13 RCT evaluating chemoablation with 40 mg/40 mL of intravesical MMC three times a week for 2 weeks without preceding biopsy to standard TURB, the 12-month RFS was 36% in the chemoablation group vs. 43% in the TURB group, with no statistical significant difference [376]. Despite the lack of long-term outcomes, chemoablation appears to be a promising treatment option for well-selected NMIBC patients and can potentially help avoid unnecessary TURB, specifically in some elderly patients with intermediate-risk NMIBC [377].

7.6 Radical cystectomy for non-muscle-invasive bladder cancer

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 [180, 378-382].
- Some patients with NMIBC experience disease progression to muscle-invasive disease (Table 6.2).
- Patients who experience disease progression to muscle-invasive stage have a worse prognosis than those who present with 'primary' muscle-invasive disease [383, 384].

The potential benefit of RC must be weighed against its risks, morbidity, and impact on quality of life (QoL) and discussed with patients, in a shared decision-making process. It is reasonable to propose immediate RC in those patients with NMIBC who are at very high risk of disease progression (see Section 6.3 and Tables 6.1 and 6.2) [73, 177, 221, 223, 385].

Early RC is strongly recommended in patients with BCG-unresponsive tumours and should be considered in BCG relapsing HG tumours as mentioned in Section 7.9 and Table 7.3. A delay in RC may lead to decreased disease-specific survival [386].

In patients in whom RC is performed before progression to MIBC, the 5-year DFS rate exceeds 80% [387-389].

7.7 Primary treatment by disease type

The type of further therapy after TURB should be based on the risk groups shown in Section 6.3 and Table 6.1. The stratification and treatment recommendations are primarily based on the risk of disease progression (Table 6.2). In some instances, mainly in intermediate-risk tumours, the 2006 EORTC scoring model is useful (Section 6.1.1.1) to determine a patient's individual risk of disease recurrence as the basis to decide further treatment on.

- Treatment of low-risk disease
  Patients in the low-risk group have a negligible risk of disease progression. The single post-operative instillation of chemotherapy reduces the risk of recurrence and is considered as sufficient treatment in these patients.

- Treatment of intermediate-risk disease
  Patients in the intermediate-risk group have a relatively low risk of disease progression (7.4 and 8.5% after 10 years according to the 2021 EAU NMIBC scoring model). In these patients induction chemotherapy with or without maintenance for a maximum of one year is a reasonable first-line option in the majority of patients. One-year full-dose BCG treatment (induction plus 3-weekly instillations at 3, 6 and 12 months), is an alternative option. 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.

- Treatment of high-risk disease
  Patients in the high-risk group have a high risk of disease progression (14% after 10 years according to the 2021 EAU NMIBC scoring model). In these patients full-dose intravesical BCG for one to 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, side effects and problems associated with BCG shortage. Because of the high risk of progression, immediate RC may also be discussed with the patient. Radical cystectomy is the safest approach from an oncological point of view, it is, however, associated with the risk of complications and QoL impairment and represents over-treatment in some patients.

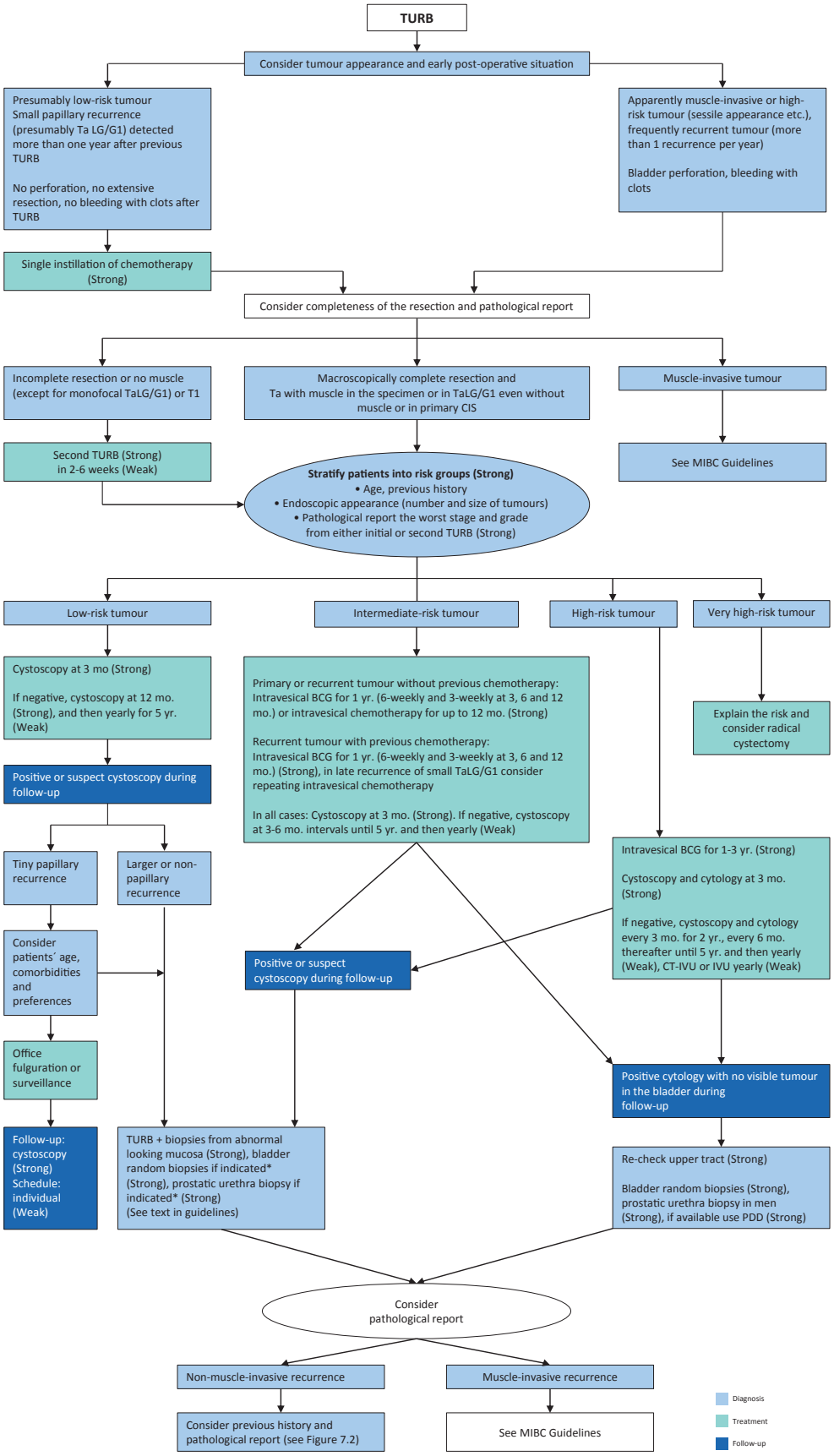
- Treatment of very high-risk disease
  Patients in the very high-risk group have an extremely high risk of tumour progression (53.1 and 58.6% after 10 years according to the 2021 EAU NMIBC scoring model). Immediate RC should be discussed with these patients. In case RC is not feasible or refused by the patient, full-dose intravesical BCG for one to 3 years should be offered.

- Treatment of carcinoma *in situ*
  Patients with carcinoma *in situ* cannot be managed by an endoscopic procedure alone and should be offered either intravesical BCG instillations or RC. 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. In comparison, immediate RC for CIS results in excellent tumour-specific survival rates although a large proportion of patients might be over-treated [232].

7.8 Multidisciplinary tumour board

A multidisciplinary tumour board (MDT) approach including reassessment of radiology and pathology is associated with a changed treatment plan in up to 44% of BC patients [390-393], such as refraining from or recommending cystectomy in 7% of stage T1 patients [391-393], often as a result of the pathologic review [68, 392]. Thus, patients with high-risk and very high-risk NMIBC will especially benefit from MDT discussion and such an approach is recommended for these patients. Figure 7.1 presents a treatment flow chart based on risk category, which may guide management of an individual patient.

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



** For details and explanations see the text of the guidelines.*
BCG = bacillus Calmette-Guérin; CIS = carcinoma in situ; CT = computed tomography; IVU = intravenous urography; MIBC = muscle-invasive bladder cancer; PDD = photodynamic diagnosis; TURB = transurethral resection of the bladder.

7.9 Treatment of failure of intravesical therapy

7.9.1 Recurrence during or after intravesical chemotherapy

Patients with NMIBC recurrence during or after a chemotherapy regimen can benefit from BCG instillations. Prior intravesical chemotherapy has no impact on the effect of BCG instillations [285].

7.9.2 Treatment failure after intravesical BCG immunotherapy

Several categories of BCG failures, broadly defined as any HG disease occurring during or after BCG therapy, have been proposed (see Table 7.2). Non-muscle-invasive BC may not respond at all (BCG refractory) or may relapse after initial response (BCG relapsing). Some evidence suggests that patients with BCG relapse have better outcomes than BCG refractory patients [394].

To be able to specify the subgroup of patients where additional BCG is unlikely to provide benefit, the category of **BCG-unresponsive** tumour was defined. Further BCG instillations in these patients are associated with an increased risk of progression [236, 395]. The category of BCG-unresponsive tumours comprises BCG-refractory and some of BCG-relapsing tumours (see Table 7.2) [396]. The definition was developed in consultation with the U.S. Food and Drug Administration (FDA), in particular to promote single-arm trials to provide primary evidence of effectiveness in this setting [397]. Patients who experience recurrence with high-grade NMIBC after BCG without meeting BCG-unresponsive criteria may benefit from additional BCG therapy. This category of high risk patients that lies between BCG-naïve and BCG-unresponsive NMIBC is termed **BCG-exposed** [398, 399], and includes:

1. BCG-resistant: persistent or recurrent Ta HG and/or CIS disease at three months following at least five of six doses of induction BCG. According to the definition of adequate BCG (table 7.2), these patients have received inadequate BCG.
2. Delayed relapse after inadequate BCG: to indicate Ta/T1 HG or CIS patients found disease free at the three-months evaluation that recur in between 6 and 24 months without receiving more than an induction course.
3. Delayed relapse after adequate BCG: to indicate patients that are disease free after adequate BCG, but subsequently experience a high-grade recurrence outside of the BCG-unresponsive window (>6 mo for Ta/T1 and >12 mo for CIS), up to 24 months.

Non-HG recurrence after BCG is not considered as BCG failure.

Table 7.2: Categories of high-grade recurrence during or after BCG

Whenever a MIBC is detected during follow-up.
BCG-refractory tumour
1. If T1 HG/G3 tumour is present at 3 months [236, 395, 400]. 2. If Ta HG/G3 tumour is present after 3 months and/or at 6 months, after either re-induction or first course of maintenance [368]. 3. If CIS (without concomitant papillary tumour) is present at 3 months and persists at 6 months after either re-induction or first course of maintenance. If patients with CIS present at 3 months, an additional BCG course can achieve a complete response in > 50% of cases [65, 364, 368]. 4. If HG tumour appears during BCG maintenance therapy*.
BCG-relapsing tumour
Recurrence of HG/G3) tumour after completion of BCG maintenance, despite an initial response [401].
BCG-unresponsive tumour
BCG-unresponsive tumours include all BCG refractory tumours and those who develop T1/Ta HG recurrence within 6 months of completion of adequate BCG exposure** or develop CIS within 12 months of completion of adequate BCG exposure [396].
BCG-exposed tumour [398, 399]
1. If Ta HG/G3 or CIS is present at three months evaluation after induction BCG only 2. delayed relapse after adequate or inadequate BCG
BCG intolerance
Severe side effects that prevent further BCG instillation before completing treatment [337].

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

*** Adequate BCG is defined as the completion of at least 5 of 6 doses of an initial induction course plus at least 2 out of 6 doses of a second induction course or 2 out of 3 doses of maintenance therapy.*

7.9.3 ***Treatment of BCG-unresponsive tumours, BCG-exposed tumours, BCG relapses and LG recurrences after BCG treatment***

Patients with BCG-unresponsive disease are unlikely to respond to further BCG therapy; RC is therefore the standard and preferred option. Currently, several bladder preservation strategies are being investigated such as cytotoxic intravesical therapies [402-405], device assisted instillations [406-408], intravesical immunotherapy [409, 410], combination therapies (mainly sequential chemotherapies see section 7.4.4.3), systemic immunotherapy [411] or gene therapy [412-414].

A phase III RCT including predominantly high-risk NMIBC patients failing at least a previous induction course of BCG, MMC combined with microwave-induced hyperthermia provided 35% overall DFS at 2 years as compared to 41% in the control arm (treated with either BCG, MMC or MMC and electromotive drug administration at the discretion of the investigator). In the pre-planned sub-analysis, MMC and microwave- induced thermotherapy showed lower response rates in CIS recurrences but higher DFS in non-CIS papillary tumours (53% vs. 24%) [408].

Promising data on BCG-unresponsive cohorts of patients with CIS alone or concomitant to papillary tumours were recently reported following new immunotherapies. Systemic pembrolizumab achieved a 40% complete response rate in a prospective phase II study which was maintained in 48% of patients for up to 12 months (n = 101), resulting in FDA approval of the study drug for this patient population [415]. Promising data from a phase III multicentre RCT with intravesical nadofaragene firadenovec showed a complete response in 53.4% of patients with BCG-unresponsive CIS which was maintained in 45% at one year in those who initially responded [416]. A secondary analysis indicates that a combination of post- treatment titres of serum anti–human adenovirus type-5 antibody and fold change from baseline can predict treatment efficacy [417]. Additional ongoing studies are addressing combination of intravesical or systemic immunotherapy [418, 419].

A systematic review and meta-analysis including 4 RCTs and 24 single-arm studies (all currently available prospective studies) assessed bladder-sparing treatments following BCG failure [420]. The significant heterogeneity of both trial designs and patient characteristics included in these studies, the different definitions of BCG failures used, and missing information on prior BCG courses may account for the variability in efficacy for the different compounds assessed across different trials. A higher number of previous BCG courses, BCG refractory/unresponsive or CIS predicted lower response rates. The pooled 12-month response rates were 24% for trials with > 2 prior BCG courses and 36% for those with > 1 BCG courses. Initial response rate did not predict durable responses highlighting the need for longer-term follow-up. More recently, a systematic review assessing 42 prospective trials on bladder-preserving treatments after BCG showed that patients with papillary-only recurrences appeared more effectively treated (median recurrence free rate of 44% at 1 year, median progression-free rate of 89% at a median follow-up of 19 months) than CIS-containing tumours (median complete response rate of 17% at 1 year with a median progression-free rate of 95% at a median follow-up of 12 months), highlighting potential biological differences between these two tumour entities which should be analysed separately when reporting results of clinical trials [421].

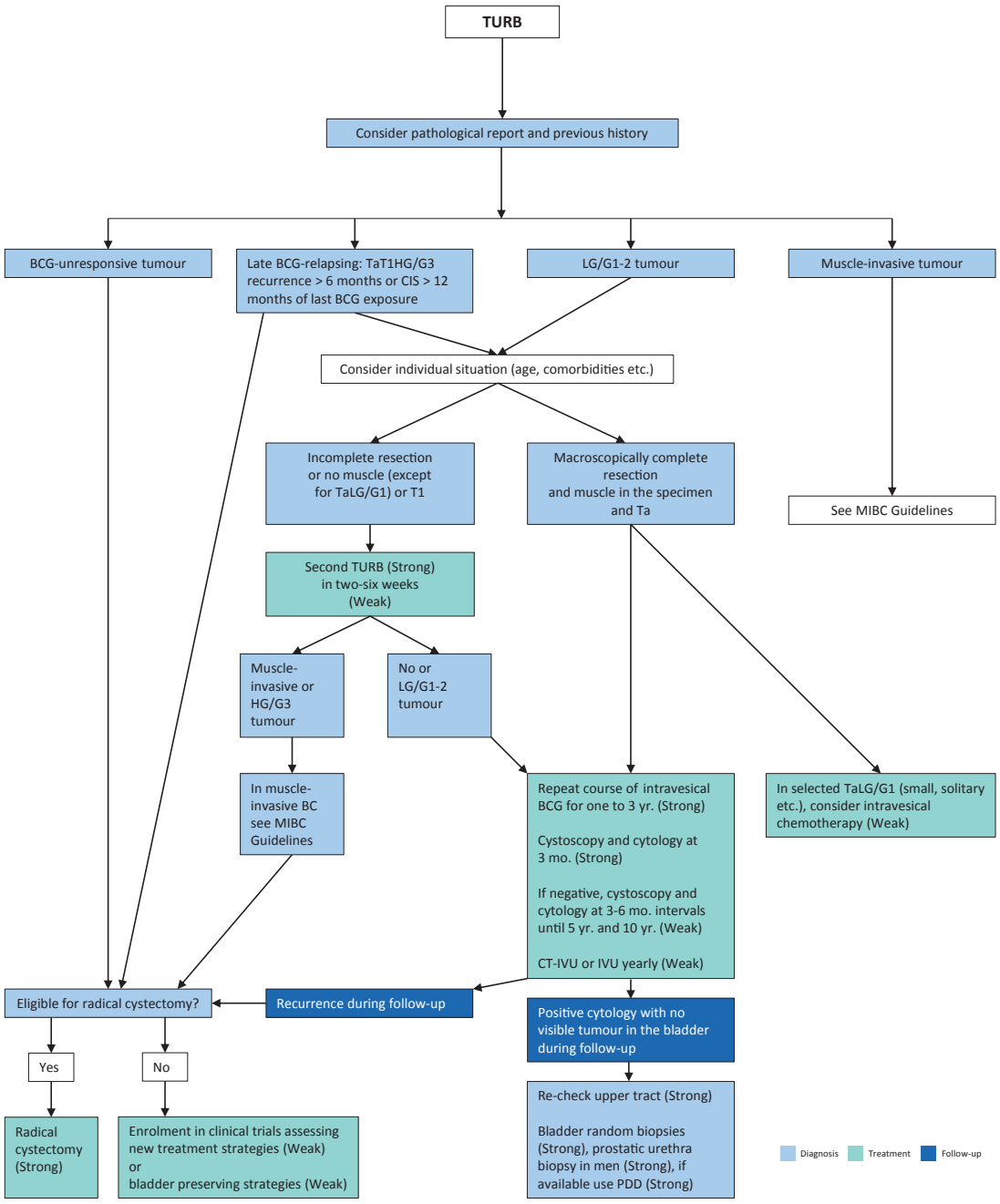
At the present time, treatments other than RC are considered oncologically inferior in patients with BCG-unresponsive disease [236, 395, 400]. Various studies suggest that repeat-BCG therapy is appropriate for non-HG and even for some HG recurrent tumours; namely those relapsing beyond one year after BCG exposure (cases which do not meet the criteria of BCG-unresponsive disease) [399, 422]. BCG exposed patients and late BCG relapses (beyond 24 months) are likely to benefit from further BCG [398, 399].

Treatment decisions in LG recurrences after BCG (which are not considered as any category of BCG failure) should be individualised according to tumour characteristics. Little is known about the optimal treatment in patients with high-risk tumours who could not complete BCG instillations because of intolerance.

7.9.4 ***Summary of evidence - treatment failure of intravesical therapy***

Summary of evidence	**LE**
Prior intravesical chemotherapy has no impact on the effect of BCG instillation.	1a
Treatments other than RC must be considered oncologically inferior in patients with BCG-unresponsive tumours.	3

Figure 7.2: Treatment strategy in recurrence during or after intravesical BCG



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

7.10 Guidelines for adjuvant therapy in TaT1 tumours and for therapy of carcinoma *in situ*

General recommendations	Strength rating
Counsel smokers to stop smoking.	Strong
The type of further therapy after transurethral resection of the bladder (TURB) should be based on the risk groups shown in Section 6.3 and Table 6.1. For determination of a patient's risk group use the 2021 EAU risk group calculator available at www.nmibc.net.	Strong
In patients with tumours presumed to be at low risk and in those with small papillary recurrences (presumably Ta LG/G1) detected more than one year after previous TURB, offer one immediate single chemotherapy instillation.	Strong
Offer post-operative saline or water continuous irrigation of the bladder to patients who cannot receive a single instillation of chemotherapy.	Strong
Patients with small recurrent low-grade Ta tumours can be effectively and safely offered office fulguration.	Strong
Only offer active surveillance to selected patients with presumed low-grade tumours not amendable to endoscopic ablation.	Weak
In patients with intermediate-risk tumours (with or without immediate instillation), offer instillations of chemotherapy (the optimal schedule is not known) or one-year full-dose Bacillus Calmette-Guérin (BCG) treatment (induction plus 3-weekly instillations at 3, 6 and 12 months). Chemotherapy is a reasonable first option in the majority of cases; however, the final choice should be made in a shared decision-making process with the patient, reflecting his/her risk of recurrence and progression, as well as the efficacy and side effects of each treatment modality.	Strong
Administer a full-dose intravesical bacillus Calmette-Guérin (BCG) for one to three years in patients with high-risk tumours (a complete BCG schedule comprises an induction phase of six-weekly instillations, followed by a maintenance phase of three-weekly instillations at 3, 6, 12, 18, 24, 30 and 36 months, respectively). The additional beneficial effect of the second and third years of maintenance should be weighed against its added costs, side effects and access to BCG. Immediate radical cystectomy (RC) may also be discussed with the patient.	Strong
Discuss immediate RC in patients with very high-risk tumours. Intravesical full-dose BCG instillations for one to three years remains an option for selected patients, particularly those who decline or are unfit for RC.	Strong
Offer transurethral resection of the prostate, followed by intravesical instillation of BCG to patients with CIS in the epithelial lining of the prostatic urethra if a bladder sparing strategy is considered.	Weak
Cautiously offer quinolones to treat BCG-related side effects*.	Weak
The definition of 'BCG-unresponsive' should be respected as it most precisely defines the patients who are unlikely to respond to further BCG instillations.	Strong
Offer a RC to patients with BCG-unresponsive tumours.	Strong
Offer patients with BCG-unresponsive tumours, who are not candidates for RC due to comorbidities, preservation strategies (intravesical chemotherapy, chemotherapy and microwave-induced hyperthermia, electromotive administration of chemotherapy, intravesical- or systemic immunotherapy; preferably within clinical trials).	Weak
Discuss high-risk and very high-risk patients within a multidisciplinary board, when possible.	Weak
Recommendations - technical aspects for treatment	
Intravesical chemotherapy	
If given, administer a single immediate instillation of chemotherapy within 24 hours after TURB.	Weak
Omit a single immediate instillation of chemotherapy in any case of overt or suspected bladder perforation or bleeding requiring bladder irrigation.	Strong

The optimal schedule and duration of further intravesical chemotherapy instillation is not defined; however, it should not exceed one year.	Weak
If intravesical chemotherapy is given, use the drug at its optimal pH and maintain the concentration of the drug by reducing fluid intake before and during instillation.	Strong
The length of individual instillation should be a minimum of one, and up to two hours.	Weak
BCG intravesical immunotherapy	
Absolute contraindications of BCG intravesical instillation are: • during the first two weeks after TURB; • in patients with visible haematuria; • after traumatic catheterisation; • in patients with symptomatic urinary tract infection.	Strong

**The side-effect profile of quinolones and fluoroquinolones resulted in the adoption of European regulation restricting their use [341].*

7.11 Guidelines for the treatment of TaT1 tumours and carcinoma *in situ* according to risk stratification

Recommendations	Strength rating
EAU risk group: Low	
Offer one immediate instillation of intravesical chemotherapy after transurethral resection of the bladder (TURB).	Strong
EAU Risk Group: Intermediate	
In general, chemotherapy (the optimal schedule is unknown) is a reasonable first-line option in the majority of patients. One-year full-dose BCG treatment (induction plus three-weekly instillations at 3, 6 and 12 months), is an alternative option. 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. Offer one immediate chemotherapy instillation to patients with small papillary recurrences detected more than one year after previous TURB.	Strong
EAU risk group: High	
Offer intravesical full-dose BCG instillations for one to three years but discuss immediate radical cystectomy (RC).	Strong
EAU risk group: Very High	
Offer RC or intravesical full-dose BCG instillations for one to three years, particularly to those who decline or are unfit for RC.	Strong

Table 7.3: Treatment options for the various categories of BCG failure

Category	Treatment options
BCG-unresponsive	1. Radical cystectomy (RC). 2. Enrolment in clinical trials assessing new treatment strategies. 3. Bladder-preserving strategies in patients unsuitable or refusing RC.
Late BCG relapsing: TaT1 HG recurrence > 6 months or CIS > 12 months of last BCG exposure	1. Radical cystectomy or repeat BCG course according to a patient's individual situation. 2. Bladder-preserving strategies. 3. Enrolment in clinical trials assessing new treatment strategies.
LG recurrence after BCG for primary intermediate-risk tumour	1. Repeat BCG or intravesical chemotherapy. 2. Enrolment in clinical trials assessing new treatment strategies.

8. FOLLOW-UP OF PATIENTS WITH NMIBC

Due to the risk of recurrence and progression, patients with NMIBC need follow-up after treatment. The first cystoscopy after TURB at 3 months is an important prognostic indicator for recurrence and progression [230, 235, 250, 253, 423]. Therefore, the first cystoscopy should always be performed 3 months after TURB in all patients with TaT1 tumours and CIS. The subsequent frequency and duration of cystoscopy and imaging follow-up should reflect the individual patient's degree of risk. This can be defined by using the EAU NMIBC prognostic factor risk groups (section 6.3, Tables 6.1 and 6.2) or further prognostic models for specific patient populations (section 6) which predict, the short- and long- term risks of recurrence and progression in individual patients (section 8.1) [221, 223]. However, recommendations for follow-up are mainly based on retrospective data and there is a lack of RCTs investigating the possibility of safely reducing the frequency of follow-up cystoscopy.

8.1 Intravesical surveillance during follow-up

*8.1.1 **Follow-up of low-risk NMIBC***

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 [252, 424]. In addition, recurrence after 5 recurrence-free years is low [253] (LE: 3). Therefore, in low-risk tumours, after 5 years of follow-up, discontinuation of cystoscopy or its replacement with less invasive methods should be considered [423].

*8.1.2 **Follow-up of intermediate-risk NMIBC***

Patients in the intermediate-risk group carry a risk of progression somewhere in between the low and high risk categories [227]; therefore, the intensity of any follow-up scheme could be adapted in line with this. Based on the safety of a reduced intensity follow-up scheme compared to high-risk NMIBC, in a small RCT on multiple and/or recurrent low grade tumours [425], low-grade intermediate-risk NMIBC can be safely followed-up with a cystoscopy at 3 months and, if negative, with 6 monthly cystoscopies for 2 years followed by yearly cystoscopies up to 10 years. This surveillance scheme for this disease category has already been adopted by the Scottish Access Collaborative Workstream [426]. Due to lack of data supporting the safety of a reduced scheme in the subgroup of high-grade intermediate-risk NMIBC the panel recommend this group be followed-up in the same way of high-risk NMIBC.

*8.1.3 **Follow-up of high- and very high-risk NMIBC***

In tumours originally, high risk, or very high risk treated conservatively the prompt detection of muscle-invasive and HG/G3 non-muscle-invasive recurrence is crucial and the percentage of tumours missed should be as low as possible because a delay in diagnosis and therapy can be life-threatening. Therefore, the best surveillance strategy for these patients will continue to include frequent cystoscopy and cytology. Recurrences after ten years tumour-free are not unusual [427]. Therefore, the optimal surveillance strategy for these patients includes initial frequent cystoscopy and cytology and life-long follow-up [423].

*8.1.4 **Follow-up of extravesical sites urothelium***

The follow-up strategy must reflect the risk of extravesical recurrence (prostatic urethra in men and UUT in both genders). This risk becomes significant for both sites in high-risk tumours [94], with 10 year tumour rates in UUT varing between 2.8% in CIS [428] and 25% in patients with multiple and recurrent high risk NMIBC [429]. Urine cytology, cystoscopy and CT urography are key investigations for early detection of extravesical recurrence.

*8.1.5 **Aids for tumour detection during follow-up***

8.1.5.1 Enhanced visualisation

There may be a role for newer methods of tumour visualisation in follow-up cystoscopy. In two prospective studies of blue light flexible cystoscopy (BLFC) for surveillance of NMIBC, BLFC allowed identification of 4 to 5.7% of recurrences that would have been missed in case of WL cystoscopy alone [430, 431]. On the other hand, a prospective study of NBI for NMIBC surveillance failed to show any benefit for NBI over WL cystoscopy alone [432].

8.1.5.2 Ultrasound

In patients initially diagnosed with Ta LG/G1–2 BC, US of the bladder and/or a urinary marker may be a mode of surveillance in case cystoscopy is not possible or refused by the patient [133, 433, 434].

8.1.5.3 Urinary molecular markers and urine cytology

Non-invasive follow-up strategies include urine cytology and urinary molecular marker tests as adjunct (or companion) tests to improve detection at the time of flexible cystoscopy or as replacement tests to reduce the number of flexible cystoscopies. Research has been carried out into the usefulness of urinary cytology vs. urinary molecular markers in the follow-up of NMIBC [112, 115, 120, 130, 433, 435]. In order to reduce or replace cystoscopy altogether, urinary markers should be able to detect recurrence in all risk groups. However, the reported low sensitivity for LG recurrences limits their utility in this group [130, 436] although more recent studies have shown reasonable sensitivity in low grade recurrences sensitivity of 40–65% [118, 437]. According to current knowledge, no urinary marker can replace cystoscopy during follow-up or lower cystoscopy frequency in a routine fashion. Nonetheless, some urinary markers have shown fairly high sensitivities to detect tumour recurrence, particularly in HG disease, along with very high NPVs to make the premises for their future implementation in follow-up [117, 437-439] (Table 8.1).

Table 8.1: Urinary markers in the surveillance setting*

Marker	Sensitivity overall	HG	Specificity overall	HG	PPV overall	HG	NPV overall	HG	N studies/ patients
XPERT BC® MONITOR	0.72	0.88	0.76	0.75	0.43	0.18	0.92	0.99	10/> 2000
EpiCheck™	0.74	0.91	0.84	0.81	0.48	0.43	0.94	0.98	5/1600
ADX Bladder™	0.57	0.71	0.62	0.76	0.29	0.37	0.82	0.93	3/1600
CX BLADDER	0.91	-	0.61	-	0.16	-	0.98	-	2/1000
FDFGR3+TERT	0.93	-	0.79	-	0.67	-	0.96	-	2/250

**Data extracted from a pooled analyses of systematic review [435].*
HG = high grade; NMIBC = non-muscle-invasive bladder cancer; PPV = positive predictive value; NPV = negative predictive value; n = number.

Table 8.2: Proposed follow-up schedule based on patient's risk category

Risk group	Cytology*	Cystoscopy	Imaging	Duration of follow-up
Low	No	At 3 and 12 months Then annually	Not systematic	5 years
Intermediate (not including HG/G3 subgroup)*	No	At 3 months Then every 6 months for 2 years Then annually	Not systematic	10 years
High and Very High	Yes**	Every 3 months for 2 years Then every 6 months up to 5 years Then annually	CT annually up to 5 years Then CT every 2 years up to 10 years	Life long

**Intermediate-risk HG/G3 subgroup should be followed-up as high-risk*
*** At the same intervals as cystoscopy*

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

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

Recommendations	Strength rating
Base follow-up of TaT1 tumours and carcinoma *in situ* (CIS) on regular cystoscopy.	Strong
Patients with low-risk Ta tumours should undergo cystoscopy at three months. If negative, subsequent cystoscopy is advised nine months later, and then yearly for five years.	Weak
Patients with high-risk and those with very high-risk tumours treated conservatively should undergo cystoscopy and urinary cytology at three months. If negative, subsequent cystoscopy and cytology should be repeated every three months for a period of two years, and every six months thereafter until five years, and then annually lifelong.	Weak
Perform cystoscopy at three months for patients with intermediate-risk Ta low-grade tumours. If negative, subsequent cystoscopy can be repeated every six months for two years, and then annually for ten years. The subgroup of intermediate-risk that are high grade should be followed up as high-risk.	Weak
Take regular and long-term upper tract imaging (computed tomography urography) for high-risk and very high-risk tumours.	Weak
Perform endoscopy under anaesthesia and bladder biopsies when office cystoscopy shows suspicious findings or if urinary cytology is positive.	Strong
During follow-up in patients with positive cytology and no visible tumour in the bladder, mapping biopsies or PDD-guided biopsies (if equipment is available) and investigation of extravesical locations (CT urography, prostatic urethra biopsy) are recommended.	Strong

9. PATIENT REPORTED OUTCOME MEASURES AND QUALITY INDICATORS FOR NMIBC

9.1 PROMS and PREMS in NMIBC

As NMIBC is associated with a significant number of hospital visits and interventions (TURBT, re-TURBT, surveillance cystoscopy, intravesical instillations) survivorship has a significant effect on patient QoL [440, 441]. Several Patient Reported Outcome Measures (PROMs) and Patient Reported Experience Measures (PREMs) have been developed to gauge the impact of treatment and surveillance on patients with a view to improving quality of care; however, due to lack of standardisation and heterogeneity none of them can currently be recommended for use in clinical practice [442]. Regardless, in order to provide the best possible care, clinicians should always be cognisant of the impact of disease and treatment (including surveillance) on their patients' QoL. The use of PROMs is an important endpoint for quality metrics and RCTs should systematically incorporate PROs for patient-centred research design.

9.2 Quality Indicators (QI) in Bladder Cancer

Evidence based Quality Indicators (QIs) and Quality Performance Indicators (QPIs) are designed to be surrogates of good practice and consequently, outcomes. They allow for the gap between efficacy and effectiveness to be narrowed, i.e. being able to bring research evidence and guideline recommendations into real world practice by improving compliance to them [443]. They also permit objective monitoring of the quality of care and thus facilitate quality control as well as service and process improvements.

Several QIs for bladder cancer have been suggested [444-447]. The table below represents the general and NMIBC related QIs adapted from Leow *et al.*, [446] and the Scottish Quality Performance Indicator (QPI) programme [447]. Quality indicators and QPIs should be SMART (Specific, Measurable, Achievable, Relevant, Trainable) [443]. Scotland introduced such a programme for Bladder Cancer in 2014 [447], and have been an exemplar by being able to demonstrate high levels of compliance to QPIs while reducing practice variation across country whilst also demonstrating the clinical value of such a programme [161], including development of prognostic models [426].

Successful implementation of a QI programme has the potential to inspire and catalyse clinical excellence in contemporary Bladder Cancer practice [443].

Table 9.1: Quality Indicators for general aspects of bladder cancer and NMIBC care adapted from [446, 447].

General aspects of bladder cancer care	Recommended Quality Indicators
Appropriate imaging for patients newly diagnosed with bladder cancer	Newly diagnosed bladder cancer patients who have cross-sectional imaging of upper urinary tract (eg, CT, MRI, or US) - as recommended in section 5.4
Participation in clinical trials	Availability of clinical trials to bladder cancer patients who are treated at a particular health care facility.
Aspects of NMIBC care	**Recommended Quality Indicators**
Pre-operative:	
Counselling	At the time of diagnosis, patients should be counselled to discontinue tobacco smoking.
Intra-operative:	
Tumour/patient history	Use of an Intra-operative checklist (as recommended in Table 5.1)
Conduct of TURBT	Patients with muscle present in specimen from initial TURBT (excluding TaLG disease).
	Use of a Bladder Diagram (as per Figure 5.1)
Re-staging TURBT	Restaging TURBT should be performed within 2–6 wk of the initial TURBT and include resection of the primary tumour site as per recommendations in section 5.13.
Post-operative:	
Risk stratification and surveillance counselling for patients with NMIBC	Use the EAU 2021 Risk Stratification for progression and the 2006 EORTC scoring model for recurrence to counsel patients with NMIBC on treatment and surveillance.
Intravesical therapy	Patients who received immediate post-TURBT instillation of intravesical chemotherapy, excluding those with contraindications (eg, incomplete resection, suspected perforation, significant haematuria).
	Intermediate- and high-risk NMIBC patients who were counselled and subsequently initiated adjuvant intravesical chemotherapy or BCG, respectively.
Multidisciplinary Team management	Patients with high risk and very high risk NMIBC should be discussed in a multi-disciplinary meeting to ensure comprehensive review and options.
Appropriate frequency of surveillance based on stage/grade of bladder cancer	Appropriate intervals between cystoscopic surveillance as per Table 8.2.
	Appropriate assessment of the upper urinary tract in high-risk patients.

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11. 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 open access available on the European Association of Urology website: https://uroweb.org/guidelines/non-muscle-invasive-bladder-cancer/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.

12. CITATION INFORMATION

The format in which to cite the EAU Guidelines will vary depending on the style guide of the journal in which the citation appears. Accordingly, the number of authors or whether, for instance, to include the publisher, location, or an ISBN number may vary.

The compilation of the complete Guidelines should be referenced as:
EAU Guidelines. Edn. presented at the EAU Annual Congress Paris 2024. ISBN 978-94-92671-23-3.

If a publisher and/or location is required, include:
EAU Guidelines Office, Arnhem, The Netherlands. http://uroweb.org/guidelines/compilations-of-all-guidelines/.

References to individual guidelines should be structured in the following way:
Contributors' names. Title of resource. Publication type. ISBN. Publisher and publisher location, year.

EAU Guidelines on

Muscle-invasive and Metastatic Bladder Cancer

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European Association of Urology

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1. INTRODUCTION

1.1 Aims and scope

This overview represents the updated European Association of Urology (EAU) Guidelines for Muscle-invasive and Metastatic Bladder Cancer (MIBC). The aim is to provide practical recommendations on the clinical management of MIBC with a focus on clinical presentation. Separate EAU guidelines are available addressing upper urinary tract (UUT) tumours [1], non-muscle-invasive bladder cancer (TaT1 and carcinoma *in situ*) (NMIBC) [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 references/individual circumstances of patients into account. Guidelines are not mandates and do not purport to be a legal standard of care.

1.2 Panel composition

The EAU Guidelines Panel consists of an international multidisciplinary group of clinicians, including urologists, oncologists, a pathologist, a radiologist, radiotherapists and patient representatives. Section 5.3 - MIBC and health status, was developed with the assistance of Prof.Dr. S. O'Hanlon, consultant geriatrician, International Society of Geriatric Oncology (SIOG) representative. 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/guidelines/muscle-invasive-and-metastatic-bladder-cancer/panel.

1.3 Available publications

A quick reference document (Pocket Guidelines) is available. This is an abridged version which may require consultation together with the full text version. Several scientific publications are available, the latest dating to 2023 [4]. 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 Guidelines on Muscle Invasive Bladder Cancer were first published in 2004. Standard procedure for EAU Guidelines includes an annual assessment of newly published literature in the field to guide future updates This 2024 MIBC Guidelines present a limited update of the 2023 publication.

*1.4.2 **Summary of changes***

For the 2024 MIBC Guidelines new and relevant evidence was identified, collated and appraised through a structured assessment of the literature for all sections of the Guidelines. Key changes include:

- new updates to the guidelines and evidence in section 5.2 on the magnetic resonance imaging for local staging of MIBC;
- new text and evidence updates in section 7.2.3 on local therapy (surgery or radiotherpy) in oligometastatic disease;
- new text and evidence updates in section 7.3.4.2 on therapeutic value of lymphadenectomy, and section 7.3.5 on robotic-assisted laparoscopic cystectomy;
- new text updates in section 7.5.2 on external beam radiotherapy;
- new text and evidence updates in section 7.5.4 on trimodality bladder-preserving treatment;
- new text, evidence and guidelines updates in section 7.7 on the management of metastatic disease.

2. METHODS

2.1 Data identification

For the 2024 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. Databases searched included Medline, EMBASE, and the Cochrane Libraries, covering a time frame between the 1st of May 2022 and 1st May 2023. A total of 1,076 unique records were

identified, retrieved and screened for relevance. A detailed search strategy is available online: https://uroweb.org/guideline/bladder-cancer-muscle-invasive-and-metastatic/?type=appendices-publications.

Recommendations within the Guidelines are developed by the panels to prioritise clinically important care decisions. The strength of each recommendation is determined by the balance between desirable and undesirable consequences of alternative management strategies, the quality of the evidence (including certainty of estimates), and the nature and variability of patient values and preferences. This decision process, which can be reviewed in the strength rating forms which accompany each guideline statement, addresses a number of key elements:

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

Strong recommendations typically indicate a high degree of evidence quality and/or a favourable balance of benefit to harm and patient preference. Weak recommendations typically indicate availability of lower quality evidence, and/or equivocal balance between benefit and harm, and uncertainty or variability of patient preference [6].

Additional methodology information and a list of associations endorsing the EAU Guidelines can be found in the online: https://uroweb.org/eau-guidelines/methodology-policies.

2.2 Peer-review

The panel intends to submit the 2025 MIBC guidelines for peer review before publication.

2.3 Future goals

Topics considered for inclusion in the 2024 update of the MIBC Guidelines:

- Development of an evidence-based strategy for functional- and oncological follow-up of patients treated for MIBC;
- Participation in developing strategies to ensure meaningful participation of patients in the development and implementation of the MIBC Guidelines.

3. EPIDEMIOLOGY, AETIOLOGY AND PATHOLOGY

3.1 Epidemiology

Bladder cancer is the 7th most commonly diagnosed cancer in males, whilst it drops to 10th position when both genders are considered [7]. The worldwide age-standardised incidence rate (per 100,000 person/years) is 9.5 for men and 2.4 for women [7]. In the European Union, the age-standardised incidence rate is 20 for men and 4.6 for women [7]. In Europe, the highest age-standardised incidence rate has been reported in Belgium (31 in men and 6.2 in women) and the lowest in Finland (18.1 in men and 4.3 in women) [7].

Worldwide, the BC age-standardised mortality rate (per 100,000 person/years) was 3.3 for men vs. 0.86 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, also partly caused by the different methodologies used in the studies and the quality of data collection [8, 9]. The incidence and mortality of BC has decreased in some registries, possibly reflecting the decreased impact of causative agents [10, 11].

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

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, 14]. 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 [15].

The incidence of BC is directly related to the duration of smoking and the number of cigarettes smoked per day [16]. A meta-analysis looked at 216 observational studies on cigarette smoking and cancer published between 1961 and 2003, and the pooled risk estimates for BC demonstrated a significant association for both current and former smokers [17]. 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]. Starting to smoke at a younger age increased the risk of death from BC [18]. An immediate decrease in the risk of BC was observed in those who stopped smoking. The reduction was about 40% within one to four years of quitting smoking and 60% after 25 years of cessation [16]. A meta-analysis of nine studies, not distinguishing between MIBC and NMIBC, suggested that smokers who decide to quit during the diagnostic work-up or upon bladder cancer diagnosis do not have a better prognosis than those who continue to smoke [19]. Nethertheless, encouraging people to stop smoking would result in the incidence of BC decreasing equally in men and women [13].

3.2.2 Occupational exposure to chemicals

Occupational exposure is the second-most important risk factor for BC. Work-related cases accounted for 20–25% of all BC cases in several series and it is likely to occur in occupations in which dyes (with the exception of hair dyes [20]), rubbers, textiles, paints, leathers, and chemicals are used [21, 22]. The risk of BC due to occupational exposure to carcinogenic aromatic amines is significantly greater after ten years or more of exposure; the mean latency period usually exceeds 30 years [23, 24]. Population-based studies established the occupational attribution for BC in men to be 7.1%, while no such attribution was discernible for women [8, 25].

3.2.3 Radiotherapy

Increased rates of secondary bladder malignancies have been reported after external-beam radiotherapy (EBRT) for gynaecological malignancies, with relative risks (RR) of 2–4 [22]. In a population-based cohort study, the standardised incidence ratios for BC developing after radical prostatectomy (RP), EBRT, brachytherapy, and EBRT-brachytherapy were 0.99, 1.42, 1.10, and 1.39, respectively, in comparison with the general U.S. population [26].

It has recently been proposed that patients who have received radiotherapy (RT) for prostate cancer with modern modalities such as intensity-modulated RT (IMRT) may have lower rates of in-field bladder- and rectal secondary malignancies [27]. 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 [27].

3.2.4 Dietary factors

Several dietary factors have been 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 an inverse association between dietary intake of flavonoids and lignans and the risk of aggressive BC tumours has been described [28].

3.2.5 Metabolic disorders

In a large prospective study pooling six cohorts from Norway, Sweden, and Austria (The Metabolic syndrome and Cancer project, Me-Can 2.0), metabolic aberrations, especially elevated blood pressure and triglycerides, were associated with increased risks of BC among men, whereas high body mass index (BMI) was associated with decreased BC risk. The associations between BMI, blood pressure and BC risk significantly differed between men and women [29].

The association of diabetes mellitus (DM) with the risk of BC has been evaluated in numerous meta-analyses with inconsistent results. When analysing specific subpopulations, DM was associated with BC or CSM risk especially in men [30]. Thiazolidinediones (pioglitazone and rosiglitazone) are oral hypoglycaemic drugs used for the management of type 2 DM. Their use and the association with BC is still a matter of debate. In a recent meta-analysis of observational studies the summary results indicated that pioglitazone use was significantly associated with an increased risk of BC which appears to be linked to higher dose and longer duration of treatment [31]. The U.S. Food and Drug Administration (FDA) recommend that healthcare professionals should not prescribe pioglitazone in patients with active BC [32]. Several countries in Europe have removed this agent

from the market or included warnings for prescription. Moreover, the benefits of glycaemic control vs. unknown risks for cancer recurrence with pioglitazone should be considered in patients with a prior history of BC.

*3.2.6 **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 [33]. There is a well-established relationship between schistosomiasis and urothelial carcinoma (UC) of the bladder, which can progress to squamous cell carcinoma (SCC), however, better control of the disease is decreasing the incidence of SCC of the bladder in endemic zones such as Egypt [34, 35].

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 [36]. However, a recent meta-analysis found no statistical association when pooling data from the most recent and highest quality studies which highlights the need for better quality data to be able to draw conclusions [37].

Similarly, urinary calculi and chronic irritation or inflammation of the urothelium have been described as possible risk factors for BC. A meta-analysis of case-control and cohort studies suggests a positive association between history of urinary calculi and BC [38].

*3.2.7 **Gender***

Although men are more likely to develop BC than women, women present with more advanced disease and have worse survival rates. A meta-analysis including nearly 28,000 patients shows that female gender was associated with a worse survival outcome (hazard ratio [HR]: 1.20, 95% CI: 1.09–1.32) compared to male gender after radical cystectomy (RC) [39]. This finding had already been presented in a descriptive nationwide analysis based on 27,773 Austrian patients. After their analysis the authors found that cancer-specific survival (CSS) was identical for pT1-tumours in both sexes, while women had a worse CSS in both age cohorts (< 70 years and ≥ 70 years) with higher tumour stages [40]. However, treatment patterns are unlikely to explain the differences in overall survival (OS) [41]. In a population-based study from the Ontario Cancer Registry analysing all patients with BC treated with cystectomy or radical RT between 1994 and 2008, no differences in OS, mortality and outcomes were found between males and females following radical therapy [42]. The gender-specific difference in survival for patients with BC was also analysed in the Norwegian population. Survival was inferior for female patients but only within the first two years after diagnosis. This discrepancy was partly attributed to a more severe T-stage in female patients at initial diagnoses [43].

A population-based study from the MarketScan Databases suggests that a possible reason for worse survival in the female population may be that women experienced longer delays in diagnosis than men, as the differential diagnosis in women includes diseases that are more prevalent than BC [44]. Furthermore, differences in the gender prevalence of BC may be due to other factors besides tobacco and chemical exposure. In a large prospective cohort study, post-menopausal status was associated with an increase in BC risk, even after adjustment for smoking status. This finding 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 [45-47]. Moreover, a recent population study assessing impact of hormones on BC suggests that younger age at menopause (≤ 45 years) is associated with an increased risk of BC [48].

*3.2.8 **Genetic factors***

There is growing evidence that genetic susceptibility factors and family association may influence the incidence of BC. A recent population-based study of cancer risk in relatives and spouses of UC patients showed an increased risk for first- and second-degree relatives, and suggests genetic or environmental roots independent of smoking-related behaviour [49]. Shared environmental exposure was recognised as a potentially confounding factor [50]. Recent studies detected genetic susceptibility with independent loci, which are associated with BC risk [51].

Genome-wide association studies (GWAS) of BC identified several susceptibility loci associated with BC risk [52, 53].

3.2.9 *Summary of evidence and guidelines for epidemiology and risk factors*

Summary of evidence	LE
Worldwide, bladder cancer is the 10th most commonly diagnosed cancer.	2a
Several risk factors associated with BC diagnosis have been identified.	3
Active and passive tobacco smoking continues to be the main risk factor, while exposure-related incidence is decreasing.	2a
The increased risk of developing BC in patients undergoing EBRT, brachytherapy, or a combination of EBRT and brachytherapy, must be considered during patient follow-up. As BC 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	Strength rating
Counsel patients to stop active and avoid passive smoking.	Strong
Inform workers in potentially hazardous workplaces of the potential carcinogenic effects of a number of recognised substances, including duration of exposure and latency periods. Protective measures are recommended.	Strong
Do not prescribe pioglitazone to patients with active bladder cancer or a history of bladder cancer.	Strong

3.3 Pathology

3.3.1 *Handling of transurethral resection and cystectomy specimens*

During transurethral resection (TUR), a specimen from the tumour and normal looking bladder wall should be taken, if possible. Specimens should be taken from the superficial and deep areas of the tumour and sent to the pathology laboratory separately, in case the outcome will impact on treatment decisions. If random biopsies of the flat mucosa are taken, each biopsy specimen of the flat mucosa should be submitted separately [54]. The sampling sites must be recorded by the urologist; the pathologist report should include location of tumour tissue in the cystectomy specimen. Anatomical tumour location is relevant for staging and prognosis [55, 56].

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 a female cystectomy specimen, the length of the urethral segment removed *en bloc* with the specimen should be checked, preferably by the urological surgeon [57].

Specimen handling should follow the general rules as published by a collaborative group of pathologists and urologists [58, 59]. 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 inked and included before fixation.

It is compulsory to study the urethra, the ureters, the prostate in men and the radial margins [60]. 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 vault (in women) have to be documented by the pathologist.

All lymph node (LN) specimens should be provided in their totality, in clearly labelled containers to allow for pTNM staging. In case of doubt or adipose differentiation of the LNs, the entire specimen is to be included. Lymph nodes should be counted and measured on slides; capsular extension and percentage of LN invasion should be reported as well as vascular embols [61, 62]. In case of metastatic spread in the perivesical fat without real LN structures (capsule, subcapsular sinus), this localisation should nevertheless be considered as N+. Potentially positive soft tissue margins should be inked by the pathologist for evaluation [63]. In rare cases, fresh frozen sections may be helpful to determine treatment strategy [64].

3.3.2 *Pathology of muscle-invasive bladder cancer*

All MIBC cases are high-grade UCs. For this reason, no prognostic information can be provided by grading MIBC [65]. Identification of morphological subtypes is important for prognostic reasons and treatment decisions [66-68].

The data presented in these guidelines are based on the 2004/2016 World Health Organization (WHO) classifications [69, 70]. An update was presented in 2022 [71].

Currently the following subtypes of UC are used [71, 72]:

1. urothelial carcinoma (more than 90% of cases);
2. urothelial carcinomas with partial squamous and/or glandular or divergent differentiation;
3. micropapillary UC;
4. nested/microcystic;
5. large nested;
6. microtubular UC;
7. plasmacytoid, signet ring;
8. lymphoepithelioma-like;
9. giant cell, diffuse, undifferentiated;
10. sarcomatoid UC;
11. some UCs with other rare differentiations;
12. urothelial carcinomas with partial NE (neuroendocrine differentiation, % to be given);
13. pure neuroendocrine carcinoma (including small and large cell neuroendocrine carcinomas [Chapter NE carcinomas in the genitourinary tract]).

In the new WHO 2022 all subtypes are considered HG [71]. The percentage of subtype in the specimen must be reported since it has been shown to be of prognostic value [73]. The majority of subtypes are MIBC, with no more than 15–30% being non-muscle invasive [73-80] (LE: 3).

3.3.3 Guidelines for the assessment of tumour specimens

Recommendations	Strength rating
Record the depth of invasion for the entire specimen (categories pT2a and pT2b, pT3a and pT3b or pT4a and pT4b).	Strong
Record margins with special attention paid to the radial margin, prostate, ureter, urethra, peritoneal fat, uterus and vaginal vault.	
Record the total number of lymph nodes (LNs), the number of positive LNs and extranodal spread.	
Record lymphovascular invasion.	
Record the presence of carcinoma *in situ*.	
Record the sampling sites as well as information on tumour size when providing specimens to the pathologist.	

*3.3.4 EAU-ESMO consensus statements on the management of advanced- and variant bladder cancer [81, 82]**

Consensus statement
Bladder UC with small cell neuroendocrine variant should be treated with neoadjuvant chemotherapy followed by consolidating local therapy.
Muscle-invasive pure SCC of the bladder should be treated with primary radical cystectomy and lymphadenectomy.
Muscle-invasive pure adenocarcinoma of the bladder should be treated with primary radical cystectomy and lymphadenectomy.
Muscle-invasive small cell neuroendocrine variant of bladder UC should not receive preventive brain irradiation to avoid brain recurrence.
Differentiating between urachal and non-urachal subtypes of adenocarcinoma is essential when making treatment decisions.
T1 high-grade bladder urothelial cancer with micropapillary histology (established after complete TURBT and/or re-TURBT) should be treated with immediate radical cystectomy and lymphadenectomy.

**Only statements which met the a priori consensus threshold across all three stakeholder groups are listed (defined as ≥ 70% agreement and ≤ 15% disagreement, or vice versa).*

4. STAGING AND CLASSIFICATION SYSTEMS

4.1 Pathological staging

For staging, the Tumour, Node, Metastasis (TNM) Classification (2017, 8th edition) is recommended [83]. Blood and lymphatic vessel invasion have an independent prognostic significance [84, 85].

4.2 Tumour, node, metastasis classification

The TNM classification of malignant tumours is the method most widely used to classify the extent of cancer spread [83] (Table 4.1).

Table 4.1: TNM Classification of urinary bladder cancer [83]

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 regional lymph nodes in the true pelvis (hypogastric, obturator, external iliac, or presacral)	
N3	Metastasis in a common iliac lymph node(s)	
M - Distant Metastasis		
M0	No distant metastasis	
	M1a	Non-regional lymph nodes
	M1b	Other distant metastasis

Staging after neoadjuvant chemotherapy (NAC) and RC can be done, but must be mentioned as ypTNM (International Collaboration on Cancer Reporting) [86]. ypT0N0 after NAC and cystectomy is associated with better prognosis [71, 87, 88].

5. DIAGNOSTIC EVALUATION

5.1 Primary diagnosis

5.1.1 Symptoms

Painless visible haematuria is the most common presenting complaint. Other presenting symptoms and clinical signs include nonvisible haematuria, 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 TUR of the bladder tumour (TURBT) to assess whether there is a palpable mass or if the tumour is fixed to the pelvic wall [89, 90]. However, considering the discrepancy between bimanual examination and pT stage after cystectomy (11% clinical overstaging and 31% clinical understaging), bimanual examination findings need to be interpreted with caution [91].

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.

Due to the high specificity of diagnostic imaging for detecting BC, patients with imaging positive for BC may avoid diagnostic flexible cystoscopy and go directly to rigid cystoscopy and transurethral resection [92, 93].

5.1.4 Urinary cytology

Examination of voided urine or bladder washings for exfoliated cancer cells has high sensitivity in high-grade tumours and is a useful indicator in cases of high-grade malignancy or CIS. However, positive urinary cytology may originate from an 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% [94, 95]. However, negative cytology does not exclude a tumour. There is no known urinary marker specific for the diagnosis of invasive BC [96].

A standardised reporting system, the 'Paris System' redefining urinary cytology diagnostic categories has been updated in 2022 [97]:

- adequacy of urine specimens (Adequacy);
- negative for high-grade UC (Negative);
- atypical urothelial cells (AUC);
- suspicious for high-grade UC (Suspicious);
- high-grade UC (HGUC).

5.1.5 Cystoscopy

Ultimately, the diagnosis of BC is made by cystoscopy and histological evaluation of resected tissue. An (outpatient) flexible cystoscopy is recommended to obtain a complete image of the bladder. However, in daily practice, If a bladder tumour has been visualised unequivocally by 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 and resection. During the procedure, a thorough inspection of the bladder with rigid cystoscopy under anaesthesia is mandatory in order not to miss any tumours at the level of the bladder neck.

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 [98]. The use of a bladder diagram is recommended.

The use of PDD could be considered if a T1 high-grade tumour is present and to identify associated CIS. Presence of CIS may lead to a modified treatment plan (see EAU Guidelines on Non-muscle-invasive Bladder Cancer [2]). Photodynamic diagnosis is highly sensitive for the detection of CIS and in experienced hands the rate of false-positive results may be similar to that with regular white-light cystoscopy [85, 99].

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 specimen.

In case MIBC is suspected, tumours need to be (ideally) 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 making a correct diagnosis and staging. In cases in which RT is considered and CIS is to be excluded, PDD can be used [100].

The involvement of the prostatic urethra and ducts in men with bladder tumours has been reported in up to 1 in 3 patients [58, 101, 102]. Under-reporting possibly also means that the exact risk is not known, but it seems to be higher if the tumour is located on the trigone or bladder neck, with concomitant bladder CIS, and in the case of multiple tumours [56, 103, 104]. 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 [105-107].

A negative urethral frozen section can reliably identify patients in whom urethrectomy should be avoided. However, a positive pre-operative biopsy seems to have limited utility as these findings are not reliably associated with final margin status [105, 108].

Diagnosis of a urethral tumour before cystectomy will result in a urethrectomy which could be a contraindication for an orthotopic diversion. However, an orthotopic diversion should not be denied based on positive pre-operative biopsy findings alone and frozen section should be part of the RC procedure, particularly in male patients [109, 110].

5.1.7 Summary of evidence and guidelines for the primary assessment of presumably invasive bladder tumours

Summary of evidence	LE
Cystoscopy is necessary for the diagnosis of bladder cancer.	1
Urinary cytology has high sensitivity in high-grade tumours including carcinoma *in situ*.	2b
In men, prostatic urethral biopsy includes resection from the bladder neck to the verumontanum (between the 5 and 7 o'clock position) using a resection loop. In case any abnormal-looking areas in the prostatic urethra are present at this time, these need to be biopsied as well.	2b

Recommendations	Strength rating
Describe all macroscopic features of the tumour (site, size, number and appearance) and mucosal abnormalities during cystoscopy. Use a bladder diagram.	Strong
Take a biopsy of the prostatic urethra in cases of bladder neck tumour, when bladder carcinoma *in situ* 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.	Strong
In men with a negative prostatic urethral biopsy undergoing subsequent orthotopic neobladder construction, an intra-operative frozen section can be omitted.	Strong
In men with a prior positive transurethral prostatic biopsy, subsequent orthotopic neobladder construction should not be denied a priori, unless an intra-operative frozen section of the distal urethral stump reveals malignancy at the level of urethral dissection.	Strong
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 cystectomy.	Strong
In the pathology report, specify the grade, depth of tumour invasion, and whether the lamina propria and muscle tissue are present in the specimen.	Strong

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

5.1.8 *EAU-ESMO consensus statements on the management of advanced- and variant bladder cancer [81, 82]**

Consensus statement
Differentiating between urachal and non-urachal subtypes of adenocarcinoma is essential when making treatment decisions.

**Only statements which met the a priori consensus threshold across all three stakeholder groups are listed (defined as ≥ 70% agreement and ≤ 15% disagreement, or vice versa).*

5.2 Imaging for staging of MIBC

In clinical practice, tumour stage and histopathological grade are used to guide treatment and determine prognosis [111-113]. Imaging is essential for local- and distant staging of BC.

The goal of imaging patients with BC is to:

- Detect bladder tumours;
- Differentiate T1 from T2 tumours as their treatment will differ;
- Determine presence of any obstruction to the upper UT;
- Evaluate the extent of locally-advanced tumour stage or tumour spread to LNs;
- Assess synchronous tumour in the upper UT or other distant organs (e.g., liver, lungs, bones, peritoneum, pleura, and adrenal glands).

Table 5.1: The role of imaging in treatment planning

Goal	Imaging modality
Differentiate T1 from T2 tumours	MRI using the Vesical Imaging Reporting and Data System [VI-RADS] score
Evaluate locally-advanced stage or spread to LNs	CT scan and MRI for abdominal- and pelvic LNs or PET/CT scan
Assess UUT or other distant organs	CT urography for evaluating the UUT and PET/CT to detect distant organ metastasis

5.2.1 *Detection*

Imaging modalities used to detect bladder tumours are: US, CT and MRI-scan. Bladder tumours are often detected as part of the haematuria work-up (including cystoscopy) or as an incidental finding on imaging.

Ultrasound can visualise intraluminal masses in the bladder and additional signs such as hydronephrosis, but cannot rule out all possible causes of haematuria. According to the results of the DETECT I trial, CT urogram can be safely replaced by renal and bladder US in patients who have non-visible haematuria [114].

5.2.2 *Local staging of the bladder and upper tract*

5.2.2.1 *Magnetic resonance imaging for local staging of MIBC*

Differentiation between NMIBC and MIBC is crucial for BC treatment. Magnetic resonance imaging has superior soft tissue contrast resolution compared with CT and can evaluate post-biopsy reaction as enhancement of the tumour occurs earlier than that of the normal bladder wall due to neovascularisation [115, 116].

The accuracy of MRI for primary tumour staging ranges from 73% to 96% (mean 85%). Huang *et al.*, in a systematic review, showed a pooled sensitivity and specificity of 90% and 88%, respectively, with results increasing to 92% and 96% when a 3T scan was used, with diffusion-weighted (DW) MRI as part of the acquisition protocol [117].

A systematic review evaluating 20 studies (n = 1,724), showed a pooled sensitivity and specificity of MRI for differentiating between stages ≤ T1 and ≥ T2 of 0.92 (95% CI: 0.88–0.95) and 0.88 (95% CI: 0.78–0.94), respectively [118]. More recently, multiparametric (mp) MRI using the VI-RADS scoring system has been introduced to differentiate between T1 vs. T2 bladder tumours with a high diagnostic accuracy [119]. The VI-RADS offers a standardised approach to both acquisition and reporting of mpMRI for BC; however, the best practice of using mpMRI in this setting and the exact cut-off levels for VI-RADS scoring still need to be determined [116]. To date, the VI-RADS score has been validated by several research groups, showing good diagnostic performance in detecting MIBC [120, 121]. Also, a high diagnostic performance for the detection of muscle invasion of urothelial carcinoma subtypes was found [122].

VI-RADS assessment scoring proved to be an independent predictor of muscle-invasiveness, which might facilitate a shift toward a more aggressive approach to selection of patients at high risk of MIBC, according to a novel proposed predictive pathway [123].

A meta-analysis found that the pooled sensitivity and specificity of mpMRI with VI-RADS acquisition and scoring for predicting MIBC were 83% and 90%, respectively [124]. The diagnostic performance of using VI-RADS scoring is similar to the diagnostic performance of a conventional bladder MRI in determining MIBC based on a previous meta-analysis of 24 studies [124]. The analysis found substantial inter-reader agreement, with kappa (κ) values ranging from 0.81 to 0.92 [124]. A systematic review and meta-analysis (n = 1,016) showed a pooled weighted mean κ estimate of 0.83 (95% CI: 0.78–0.88) [125]. The potential role of mpMRI as first-line test for local staging of BC rather than TURB has been demonstrated in a recent clinical trial [126].

A modified Delphi methodology was recently developed by a panel of highly experienced, internationally recognised radiologists, urologists, oncologists, radiation oncologists and a representative from a patient advocacy group, to provide consensus-based recommendations for urinary bladder MRI to help formulate international guidelines, particularly for pre-operative cancer staging and the assessment of the response to systemic therapy. Among several statements that reached agreement, experts recommend acquiring and interpreting MR images according to VI-RADS recommendations and always perform MRI before TURBT, if available [127].

Considering the link established between the use of gadolinium-based contrast agents and nephrogenic systemic fibrosis (NSF) in patients with impaired renal function, contrast medium should be managed according to the European Society of Urogenital Radiology (ESUR) Guidelines [128]. Interest is growing in the role of non-contrast MRI for the assessment of MIBC using VI-RADS with studies demonstrating how non-contrast-enhanced VI-RADS scoring achieved similar predictive accuracy for diagnosis of MIBC to that of conventional VI-RADS; however, further additional evidence is needed to provide any recommendation on the use of non-contrast MRI for bladder cancer staging [129].

5.2.2.2 CT imaging for local staging of MIBC

General advantages of CT imaging 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 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 increases with more advanced disease [130].

Both CT and MRI may be used for assessment of local invasion by T3b disease, or higher, but they are unable to accurately diagnose microscopic invasion of perivesical fat (T2 vs. T3a) [131]. Contrast-enhanced CT using iodinated contrast media can be considered as an alternative to MRI when MRI is contraindicated or not available [128].

5.2.2.3 Computed tomography urography for local staging of the upper tract

For local staging of the UUT, CTU has the highest diagnostic accuracy of the available imaging techniques. The sensitivity of CTU for UTUC is 0.67–1.0 and specificity is 0.93–0.99 [132].

Rapid acquisition of thin sections allows high-resolution isotropic images that can be viewed in multiple planes to assist with diagnosis without loss of resolution. Epithelial 'flat lesions' without mass effect or urothelial thickening are generally not visible with CT. The secondary sign of hydronephrosis is associated with advanced disease and poor oncological outcome [133]. The presence of enlarged LNs is highly predictive of metastases in UTUC [134].

5.2.2.4 Magnetic resonance urography for local staging of the upper tract

Magnetic resonance urography is indicated in patients who cannot undergo CTU, usually when radiation or iodinated contrast media are contraindicated [135]. The sensitivity of MR-urography is 0.75 after contrast injection for tumours < 2 cm [135]. The use of MR-urography with gadolinium-based contrast media should be limited in patients with severe renal impairment (< 30 mL/min creatinine clearance), due to the risk of NSF. Computed tomography urography is generally preferred to MR-urography for diagnosing and staging UTUC.

*5.2.3 **Distant staging of lymph nodes and other sites***

5.2.3.1 Imaging of lymph nodes in MIBC

Assessment of LN metastases based on size alone is limited; both CT and MRI are unable to identify metastases in normal-sized or minimally-enlarged nodes. The sensitivity of these modalities for detection of LN metastases is low (48–87%). Specificity is also low because nodal enlargement may be due to benign

disease. Overall, CT and MRI show similar results in the detection of LN metastases in a variety of primary pelvic tumours [135-137]. 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 [138]. In a recent paper including 1,104 patients, conventional cross-sectional imaging showed slight concordance (64.9%) between cN and pN stages (sensitivity: 30%; specificity: 84%) [139]. An artificial intelligence-assisted lymph node metastases diagnostic model (LNMDM) on whole slide images (CT, MRI and PET/CT) has been developed and applied in a cohort of 1,012 patients with bladder cancer who had radical cystectomy and pelvic lymph node dissection with the AUC for accurate diagnosis of the LNMDM ranged from 0.978 (95% CI 0.960–0.996) to 0.998 (95% CI: 0.996–1.000) in the five validation sets [140].

^{18}F-fluorodeoxy glucose-Positron emission tomography (FDG-PET) combined with CT is increasingly being used in clinical practice but its exact role still needs to be further evaluated [141, 142]. According to a systematic review and meta-analysis including 785 patients, FDG-PET/CT showed a low sensitivity and high specificity for the detection of metastatic LNs in patients with newly diagnosed BC [143]. However, most studies evaluating FDG-PET/CT for LN assessment reported higher sensitivity than CT, with comparable specificity [144]. PET/CT can provide additional information to guide local treatment in case of presence of pelvic nodes metastases [145].

However, in a clinical trial assessing the role of PET/CT in evaluating LN involvement in patients receiving neoadjuvant pembrolizumab. The performance of PET/CT did not justify its routine use in cN0 MIBC patients, but proved useful in optimising selection of MIBC patients suited for neoadjuvant immunotherapy (IO) strategies in a clinical trial setting [146]. Several studies have demonstrated the possible role of radiomics for the detection of pathological lymph nodes in bladder cancer patients; however, the level of evidence remains low.

5.2.3.2 Distant metastases

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 e.g., lung [147] and liver metastases [148], respectively.

Evidence for the role of FDG-PET/CT for staging distant metastases of MIBC is still limited. In a recent series of 711 patients, FDG-PET/CT has shown to provide important staging information through the detection of distant metastases, which may impact the clinical management of MIBC patients [145].

Bone and brain metastases are rare at the time of presentation of invasive BC. In a recent retrospective, large sample, study bone scan has been shown to have an impact on patients' intended management in only 19 out of 1,148 (1.7%) patients, therefore it should not be routinely used [149]. Whole-body MRI is more sensitive and specific for diagnosing bone metastases than bone scintigraphy [150]. Also, additional brain imaging is not routinely indicated unless the patient has specific symptoms or signs to suggest brain metastases.

*5.2.4 **Response to therapy***

Pre-operative MRI conducted in various clinical settings may provide useful information regarding treatment response. In the neoadjuvant setting, the first study evaluating the performance of MRI in assessing therapeutic response to chemotherapy showed superiority of DWI over T2-weighted and dynamic contrast-enhanced (DCE)-MRI [151]. The high specificity of DWI indicates its usefulness in accurate predicting a complete histopathological response, allowing for better patient selection for bladder-sparing protocols [152]. Dynamic contrast-enhanced MR imaging may also be useful for predicting a patient's response to chemotherapy. In addition, quantitative DWI/MRI analysis has shown to provide an accurate and non-invasive assessment of bladder RT response. However, multicentre validation is required before prospective testing to inform MIBC follow-up schedules and decision making [153].

In the previously cited consensus-based recommendations, experts agreed upon the performance on MRI to assess response to systemic therapy to select patients for radical treatment, for surveillance, and for bladder-sparing surgery [127].

A meta-analysis investigated the predictive role of 18F-FDG PET/CT for assessment of tumour response to neoadjuvant chemotherapy in a total of 278 patients, showed a pooled sensitivity of 0.84 (95% CI, 0.72–0.91), and specificity of 0.75 (95% CI, 0.59–0.86). Among the five studies, only three used both of CR and pCR as reference standard [154].

The performance of PET/CT in evaluating LN involvement in patients receiving neoadjuvant pembrolizumab did not justify its routine use in cN0 MIBC patients [146].

5.2.5 *Future perspectives*

Potential future application of the VI-RADS score may include prediction of response to treatment as well as peri-operative outcomes using its modified version: the NAC VI-RADS (nacVI-RADS), however, prospective evidence is warranted [155].

Future trends might include image analysis radiomic-based techniques in predicting MIBC. A meta-analysis (n = 860) provided summary estimates for sensitivity and specificity in predicting MIBC of 82% (95% CI: 77–86%) and 81% (95% CI: 76–85%), respectively [156].

PET/MRI combining the benefits of MRI with functional imaging could be evisioned for the detection of metastatic BC lesions not seen on CT in patients who cannot receive intravenous iodine contrast, and may lead to improved treatment planning and monitoring for BC [157].

Among the novel approaches and radiotracers, in a pilot study, Rietbergen *et al.*, showed that the sentinel node (SN) biopsy in bladder cancer using the hybrid tracer $^{ICG-\ 99mTc}$-nanocolloid is feasible, and in patients with a successful pre-operative SN mapping using lymphoscintigraphy and SPECT/CT, the intraoperative SN guidance and detection are effective, even outside the extended pelvic lymph node dissection (ePLND) area [158].

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

Summary of evidence	LE
Imaging as part of staging in muscle-invasive bladder cancer (MIBC) provides information about prognosis and assists in selection of the most appropriate treatment.	2b
The diagnosis of upper tract UC depends on CT urography and, if needed, ureteroscopy.	2b
In local staging, MRI is superior to CT in terms of differentiating T1 from T2 disease.	2b
MRI is accurate for the assessment of tumour response to systemic therapy	3
Bone scintigraphy has limited value in the staging of invasive BC.	3
FDG-PET/CT can provide additional information to guide treatment.	2b

Recommendations	Strength rating
Always perform MRI before TURBT, if available.	Weak
In patients with confirmed muscle-invasive bladder cancer, use computed tomography (CT) of the chest, abdomen and pelvis for staging, including some form of CT urography with designated phases for optimal urothelial evaluation.	Strong
Use CT urography, unless it is contraindicated for reasons related to contrast adminstration or radiation dose; in that case use magnetic resonance imaging.	Strong
Offer MRI to assess the response to systemic therapy, which aids in the selection of patients for radical treatment, surveillance, and bladder-sparing surgery.	Weak

5.3 Muscle-invasive and metastatic bladder cancer and health status

Complications from 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, although chronological age is less important than frailty [159-161]. Frailty is a syndrome of reduced ability to respond to stressors. Patients with frailty have a higher risk of mortality and negative side effects of cancer treatment [162]. Controversy remains regarding age, RC and the type of urinary diversion. Radical cystectomy is associated with the greatest risk reduction in disease-related and non-disease-related death in patients aged < 80 years [163].

The largest retrospective study on RC in septuagenarians and octogenarians based on data from the National Surgical Quality Improvement Program database (n = 1,710) showed no significant difference for wound, cardiac, or pulmonary complications. However, the risk of mortality in octogenarians compared to septuagenarians is higher (4.3% vs. 2.3%) [164]. Although some octogenarians successfully underwent a neobladder procedure, most patients were treated with an ileal conduit diversion. It is important to evaluate functioning and quality of life (QoL) of older patients using a standardised geriatric assessment, as well as carrying out a standard medical evaluation [165].

Sarcopenia has been shown to be an independent predictor for OS and CSS in a large multi-centre study with patients undergoing RC for BC [166]. In order to predict CSM after RC in patients receiving NAC, sarcopenia should be assessed after completing chemotherapy [167]. Other risk factors for morbidity include prior abdominal surgery, extravesical disease, and prior RT [168]. Female gender, an increased BMI and lower pre-operative albumin levels are associated with a higher rate of parastomal hernias [169]. Low pre-operative serum albumin is also associated with impaired wound healing, gastrointestinal (GI) complications and a decrease of recurrence-free and OS after RC [170, 171]. Therefore, it could be used as a prognostic biomarker for patients undergoing RC.

Metformin has been suggested as having possibly anticancer activity in bladder cancer by inhibiting tumour growth as well as being synergistic with Cisplatin. A systematic review and meta-analysis of 4,006 patients suggests that Metformin use was associated with lower cancer specific and overall moratlity in patients with MIBC [172].

5.3.1 Evaluation of comorbidity, frailty and cognition

Rochon *et al.*, have shown that evaluation of comorbidity provides a better indicator of life expectancy in MIBC than patient age [173]. Evaluation of comorbidity helps to identify factors likely to interfere with, or have an impact on, treatment and the evolution and prognosis of MIBC [174].

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 outcomes following RC [175]. 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 [176].

Stratifying older patients according to frailty using a multidisciplinary approach will help select patients most likely to benefit from radical surgery and to optimise treatment outcomes [177]. There are many different screening tools available for frailty and local approaches can be used. Examples include the G8 and the Clinical Frailty Scale (See Table 5.2 and Figure 5.1 below).

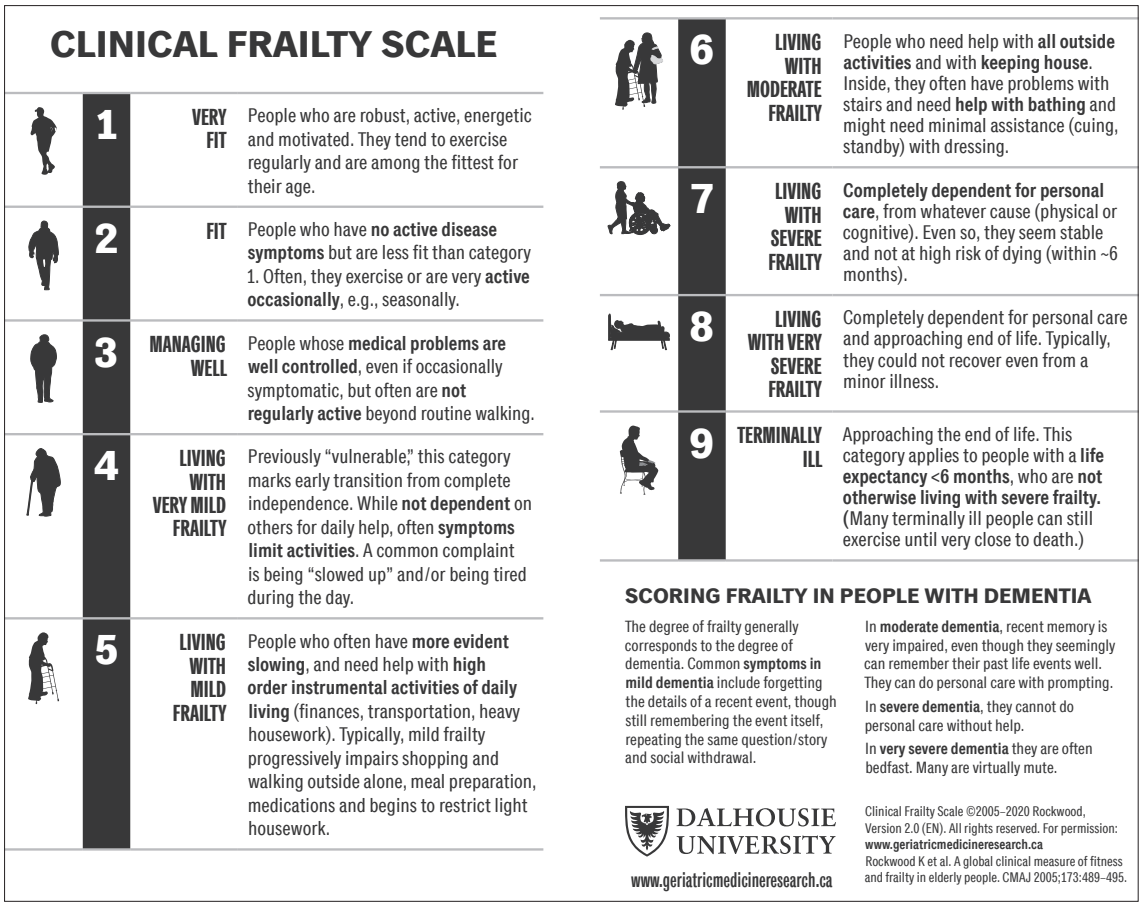
Cognitive impairment can be screened for by using a tool such as the mini-COG (https://mini-cog.com/), which consists of three-word recall and a clock-drawing test, and can be completed within 5 minutes. A score of ≤ 3/5 indicates the need to refer the patient for full cognitive assessment. Patients with any form of cognitive impairment (e.g., Alzheimer's or vascular dementia) may need a capacity assessment of their ability to make an informed decision, which is an important factor in health status assessment. Cognitive impairment also predicts risk of delirium, which is important for patients undergoing surgery [178].

Table 5.2: G8 screening tool (adapted from [179])

	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
D	Neuropsychological problems?	0 = severe dementia or depression
		1 = mild dementia
		2 = no psychological problems
E	BMI? (weight in kg)/(height in m^2)	0 = BMI < 19
		1 = BMI 19 to < 21
		2 = BMI 21 to < 23
		3 = BMI ≥ 23

F	Takes more than three prescription drugs per day?	0 = yes
		1 = no
G	In comparison with other people of the same age, how does the patient consider his/her health status?	0.0 = not as good
		0.5 = does not know
		1.0 = as good
		2.0 = better
H	Age	0 = ≥ 85
		1 = 80–85
		2 = < 80
	Total score	**0–17**

Figure 5.1: Clinical Frailty Scale©, Version 2.0* [180]



**Permission to reproduce the Clinical Frailty Scale© has been granted by the copyright holder.*

5.3.2 Comorbidity scales, anaesthetic risk classification and geriatric assessment

A range of comorbidity scales has been developed [181], seven of which have been validated [182-188]. 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 [189, 190], overall mortality [191], and CSM [163, 92-194]. Only the age-adjusted version of the CCI was correlated with both cancer-specific and other-cause mortality [195]. The age-adjusted CCI (Table 5.3) is the most widely used comorbidity index in cancer for estimating long-term survival and is easily calculated [196].

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 [197]. The Eastern Cooperative Oncology Group (ECOG) performance status (PS) scores and Karnofsky index have been validated to measure patient activity [198]. Performance score is correlated with patient OS after RC [193] and palliative chemotherapy [199-201].

Patients who have screened positive for frailty or cognitive impairment benefit from an assessment by a geriatrician. This allows identification of geriatric syndromes and any scope for optimisation. The most complete protocol is the Comprehensive Geriatric Assessment (CGA) [202] which is useful in the care of cancer patients [203]. In BC, the CGA has been used to adapt gemcitabine chemotherapy in previously untreated older patients with advanced BC [204].

Table 5.3: Calculation of the Charlson Comorbidity Index

Number of points	Conditions
1	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	61–70 years
	Hemiplegia
	Moderate to severe kidney disease
	Diabetes with organ damage
	Tumours of all origins
3	71–80 years
	Moderate to severe liver disease
4	81–90 years
5	> 90 years
6	Metastatic solid tumours
	AIDS

Interpretation:

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

5.3.3 Summary of evidence and guidelines for comorbidity scales

Summary of evidence	LE
Chronological age is of limited relevance.	3
It is important to screen for frailty and cognitive impairment and provide a Comprehensive Geriatric Assessment (CGA) where optimisation is needed.	3

Recommendations	Strength rating
Base the decision on bladder-sparing treatment or radical cystectomy in older/frail patients with invasive bladder cancer on tumour stage and frailty.	Strong
Assess comorbidity by a validated score, such as the Charlson Comorbidity Index. The American Society of Anesthesiologists score should not be used in this setting (see Section 5.3.2).	Strong

6. MARKERS

6.1 Introduction

Both patient and tumour characteristics guide treatment decisions and prognosis of patients with MIBC.

6.2 Prognostic markers

6.2.1 Histopathological and clinical markers

The most important histopathological prognostic variables after RC and LN dissection are tumour stage and LN status [205]. In addition, other histopathological parameters of the RC specimen have been associated with prognosis.

The value of lymphovascular invasion was reported in a systematic review and meta-analysis including 78,000 patients from 65 studies treated with RC for BC [206]. Lymphovascular invasion was present in 35% of the patients and correlated with a 1.5-fold higher risk of recurrence and CSM, independent of pathological stage and peri-operative chemotherapy. This correlation was even stronger in those patients with node-negative disease [207].

In a systematic review and meta-analysis including 23 studies and over 20,000 patients, the presence of concomitant CIS in the RC specimen was associated with a higher odds ratio (OR) of ureteral involvement (pooled OR: 4.51, 2.59–7.84). Concomitant CIS was not independently associated with OS, recurrence-free survival (RFS) and DSS in all patients, but in patients with organ-confined disease concomitant CIS was associated with worse RFS (pooled HR: 1.57, 1.12–2.21) and CSM (pooled HR: 1.51, 1.001–2.280) [207].

Tumour location has been associated with prognosis. Tumours located at the bladder neck or trigone of the bladder appear to have an increased likelihood of nodal metastasis (OR: 1.83, 95% CI: 1.11–2.99) and have been associated with decreased survival [205, 208-210].

Prostatic urethral involvement at the time of RC was also found to be associated with worse survival outcomes. In a series of 995 patients, prostatic involvement was recorded in 31% of patients. The 5-year CSS in patients with CIS of the prostatic urethra was 40%, whilst the prognosis of patients with UC invading the prostatic stroma was worse with a 5-year CSS of only 12% [211].

Neutrophil-to-lymphocyte ratio (NLR) has emerged as a prognostic factor in UUT tumours [1] and other non-urological malignancies. In a pooled analysis of 21 studies analysing the prognostic role of NLR in BC, the authors correlated elevated pre-treatment NLR with OS, RFS and disease-free survival (DFS) in both localised and metastatic disease [212]. In contrast, a secondary analysis of the Southwest Oncology Group (SWOG) 8710 trial, a randomised phase III trial assessing cystectomy ± NAC in patients with MIBC, suggests that NLR is neither a prognostic nor a predictive biomarker for OS in MIBC [213].

In patients with LN-positive disease, the American Joint Committee on Cancer (AJCC)-TNM staging system provides 3 subcategories. In addition, several other prognostic LN-related parameters have been reported. These include, but are not limited to, the number of positive LNs, the number of LNs removed, LN density (the ratio of positive LNs to the number of LNs removed) and extranodal extension. In a systematic review and meta-analysis, it was reported that LN density was independently associated with OS (HR: 1.45, 95%, CI: 1.11–1.90) [214]. It has been suggested that LN density outperforms the AJCC-TNM staging system for LN-positive disease in terms of prognostic value [215, 216]. However, in spite of these studies supporting the use of LN density, LN density relies on the number of LNs removed which, in turn, is subject to surgical and pathological factors. This makes the concept of LN density difficult to apply uniformly [217].

Two studies investigated whether any of the reported LN-related parameters may be superior to the routinely used AJCC-TNM staging system [217, 218]. Whilst the conclusion was that the AJCC-TNM staging system for LN status did not perform well, none of the other tested variables outperformed the AJCC system.

6.2.2 *Molecular markers*

6.2.2.1 *Molecular variants based on the Cancer Genome Atlas cohort*

The updated Cancer Genome Atlas (TCGA) reported on 412 MIBCs and identified two main groups; luminal and basal-squamous - consisting of five mRNA expression-based molecular variant including luminal- papillary, luminal-infiltrated, luminal; basal-squamous; and neuronal; a variant associated with poor survival in which part of tumours do not have small cell or neuroendocrine histology. Each variant is associated with distinct mutational profiles, histopathological features and prognostic and treatment implications [219].

The basal-squamous variant is characterised by expression of basal keratin markers, immune infiltrates and is felt to be chemosensitive. The different luminal variants are characterised by fibroblast growth factor receptor 3 (FGFR3) alterations (luminal-papillary [LumP]), epithelial-mesenchymal transition (EMT) markers (luminal-infiltrated) and may be associated with chemotherapy resistance [67, 68, 219, 220]. In 2019, a consensus on molecular variant classification was reported [221]. The authors analysed 1,750 MIBC transcriptomic profiles from 18 datasets and identified six MIBC molecular classes that reconcile all previously published classification schemes. The molecular variant classes include LumP, luminal non-specified (LumNS), luminal unstable (LumU), stroma-rich, basal/squamous (Ba/Sq), and neuroendocrine-like (NE-like). Each class has distinct differentiation patterns, oncogenic mechanisms, tumour micro-environments and histological and clinical associations. However, the authors stressed that consensus was reached for biological rather than clinical classes. Therefore, at this time, the classification should be considered as a research tool for retrospective and prospective studies until future studies establish how these molecular variants can be used best in a clinical setting.

Molecular classification of MIBC is still evolving and treatment tailored to molecular variant is not a standard yet. A novel 12-gene signature derived from patients in the TCGA utilising published gene signatures has been developed and externally validated to predict OS in MIBC [222]. Interestingly, an analysis of molecular typing in MIBC demonstrated that although molecular variants reflect the heterogeneity of bladder tumours and are associated with tumour grade, clinical parameters outperformed variants for predicting outcome [223]. In the coming years, new insights into BC carcinogenesis may change our management of the disease and our ability to better predict outcomes [224]. Outside clinical trials, molecular examination, either by expression profiling or immunohistochemistry, is not yet part of routine clinical work-up awaiting more conclusive data.

6.3 *Predictive markers*

6.3.1 *Clinical and histopathological markers*

Based on retrospective data only, patients with secondary MIBC have a worse response to NAC compared to patients with primary MIBC [225]. Pietzak *et al.*, retrospectively analysed clinico-pathologic outcomes comparing 245 patients with clinical T2–4a N0M0 primary MIBC and 43 patients with secondary MIBC treated with NAC and RC. They found that patients with secondary MIBC had lower pathologic response rates following NAC than those with primary MIBC (univariable 26% vs. 45%, multivariable OR: 0.4 [95% CI: 0.18–0.84, p = 0.02]). They also found that MIBC patients progressing after NAC had worse CSS as compared to patients treated with cystectomy alone (p = 0.002).

Subtypes and non-UC have also been linked to worse outcomes after NAC, but there is, as yet, insufficient data to conclude that they can be considered as predictive markers [226].

6.3.2 *Molecular markers*

Several predictive biomarkers have been investigated such as serum vascular endothelial growth factor (VEGF) [227], circulating tumour cells, immune and stromal signatures, as well as expression of or defects in DNA damage repair (DDR) genes including ERCC2, ATM, MRE11, RB1 and FANCC that may predict response to cisplatin-based NAC [228, 229] or chemoradiation [230-233]. More recently, alterations in FGFR2/3 including both mutations and gene fusions have been shown to be associated with response to FGFR inhibitors [234, 235].

More recent efforts have focused on markers for predicting response to immune checkpoint inhibition. Programmed death-ligand 1 (PD-L1) expression by immunohistochemistry has been evaluated in several studies with mixed results which may in part be related to the use of different antibodies and various scoring systems evaluating different compartments, i.e., tumour cells, immune cells, or both. The major limitation of PD-L1 staining relates to the significant proportion of PD-L1-negative patients that respond to immune checkpoint blockade. For example, in the IMvigor 210 phase II study of atezolizumab in patients with advanced/metastatic UC who progressed after platinum-based chemotherapy, responses were seen in 18% of patients with low/no PD-L1 expression [236]. At present, the only indication for PD-L1 testing relates to the use of immune checkpoint inhibitors as monotherapy in patients with locally-advanced or metastatic UC unfit for cisplatin-containing chemotherapy who have not received prior therapy. In this setting, atezolizumab (the European Medicines Agency [EMA] approval) or pembrolizumab (EMA approval) should only be used in patients unfit for cisplatin-containing chemotherapy whose tumours overexpress PD-L1 (i.e., in case of atezolizumab; tumour-

infiltrating immune cells [IC] covering ≥ 5% of the tumour area using the SP142 assay; in case of pembrolizumab, a combined positive score (CPS) of ≥ 10 using the Dako 22C33 platform) [237]. The FDA revised the label for pembrolizumab in patients with advanced UC with approval in first line only for patients not eligible for any platinum-based chemotherapy, however, irrespective of PD-L1 status.

Urothelial cancer is associated with a high tumour mutational burden (TMB) [238]. Both predicted neoantigen burden and TMB have been associated with response to immune checkpoint blockade in several malignancies. High TMB has been associated with response to immune checkpoint inhibitors in metastatic BC [236, 239]. Conflicting results have been seen in studies evaluating immune checkpoint inhibitors in the neoadjuvant setting with the Pembrolizumab as Neoadjuvant Therapy Before Radical Cystectomy in Patients With Muscle- Invasive Urothelial Bladder Carcinoma (PURE)-01 study demonstrating an association of high TMB with response while there was no association with atezolizumab in the Phase II study investigating the safety and efficacy of neoadjuvant atezolizumab in MIBC (ABACUS) [240, 241].

Other markers that have been evaluated in predicting response to immune checkpoint inhibitors include molecular subtypes as discussed earlier, CD8 expression by immunohistochemistry and other immune gene cell signatures. Recent work has focused on the importance of stroma including the role of transforming growth factors (TGFs) in predicting response to immune checkpoint blockade [242, 243]. Powles *et al.*, have reported on the potential for ctDNA to guide the use of adjuvant IO in UC [244]. In 581 patients from a phase III RCT of adjuvant atezolizumab vs. observation in UC, ctDNA testing at the start of therapy identified 214 (37%) patients who were positive for ctDNA and who had poor prognosis (observation arm HR = 6.3, 95% CI: 4.45–8.92; p < 0.0001). Patients who were positive for ctDNA had improved DFS and OS in the atezolizumab arm vs. the observation arm (DFS: HR = 0.58 [95% CI: 0.43–0.79]; p = 0.0024, OS: HR = 0.59 [95% CI: 0.41–0.86]). There was no difference in DFS or OS between treatment arms for patients who were negative for ctDNA. The rate of ctDNA clearance at week 6 was higher in the atezolizumab arm (18%) than in the observation arm (4%) (p = 0.0204). An ongoing clinical trial (IMvigor011) is evaluating atezolizumab as adjuvant therapy in patients with high-risk MIBC who are ctDNA positive following cystectomy [245].

A exploratory analysis in patients with metastatic UC who received pembrolizumab in the first-line (KEYNOTE-052 trial) and salvage (KEYNOTE-045 trial) settings, demonstrated that TMB and T-cell inflammed gene expression profile were significantly associated with improved outcomes, however PD-L1 was associated with improved outcomes and stromal signature with worse outcomes in KEYNOTE-052, but not KEYNOTE-045 suggesting that these biomarkers may perform differently in different clinical disease states i.e. first line versus salvage settings [246]. In a second study, a scoring system (CPT) based on CD39, PD-L1 and TMB was shown to predict response to PD-L1 blockade and platinum-based chemotherapy in patients with MIBC [247].

Although promising, there are currently no validated predictive molecular markers that are routinely used in clinical practice. Further validation studies are awaited.

6.4 Conclusion

The updated TCGA and other efforts have refined our understanding of the molecular underpinnings of BC biology. Molecular variants, immune gene signatures as well as stromal signatures may ultimately have an important role in predicting response to IO. Although PD-L1 expression by immunohistochemistry and TMB have demonstrated predictive value in certain settings, additional studies are needed. Prospectively validated prognostic and predictive molecular biomarkers will present valuable adjuncts to clinical and pathological data, but large phase III RCTs with long-term follow-up will be needed to clarify the many questions remaining.

6.5 *Summary of evidence for urothelial markers*

Summary of evidence	LE
There is insufficient evidence to use TMB, molecular variants , immune- or other gene expression signatures for the management of patients with urothelial cancer.	NR

7. DISEASE MANAGEMENT

7.1 Neoadjuvant therapy

7.1.1 Introduction

The standard treatment for patients with urothelial MIBC and MIBC with subtypes is RC. However, RC only provides 5-year survival in about 50% of patients [248-250]. To improve survival in patients with cN0M0 disease, cisplatin-based NAC has been used since the 1980s [248-252].

7.1.2 Role of cisplatin-based chemotherapy

There are theoretical advantages and disadvantages of administering chemotherapy before planned definitive surgery to patients with resectable muscle-invasive cN0M0 UC of the bladder:

- 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 may respond to NAC and have a favourable pathological response as determined mainly by achieving ypT0, ≤ ypT1, ypN0 and negative surgical margins. An analysis to identify the optimal definition of pathological response reported a significantly higher risk of recurrence in patients with ypTaN0 or ypT1N0 disease (with or without Tis) at RC and thus proposed that optimal pathological response after NAC be defined as attainment of ypT0N0/ypTisN0 at RC [253].
- Delayed cystectomy might compromise the outcome in patients not sensitive to chemotherapy [254-256]. A comparative survival analysis of patients treated with NAC and RC vs. RC alone based on data from the U.S. National Cancer Database showed that organ-confined disease (≤ pT2) after NAC was associated with decreased risk of death (HR: 0.85, 95% CI: 0.79–0.91) compared to RC alone, whereas > pT2 was associated with increased risk of death (HR: 1.46, 95% CI: 1.34–1.60) [257]. However, there are no prospective trials indicating that delayed surgery due to NAC has a negative impact on survival. In the phase III VESPER trial, comparing gemcitabine/cisplatin (GC) vs. high-dose-intensity methotrexate, vinblastine, doxorubicine and cisplatin (HD-MVAC) in the peri-operative setting, approximately 90% of patients proceeded to surgery (with median delay of 48 days for GC and 51 days for dd-MVAC) [258].
- Neoadjuvant chemotherapy does not seem to affect the outcome of surgical morbidity. In a recently reported large multicenter retrospective analysis, NAC did not lead to an increased risk of post-operative complications after RC [259]. 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 with 71% of patients receiving all three chemotherapy cycles [260].
- Clinical staging using bimanual palpation, CT or MRI may result in over- and understaging and have a staging accuracy of only 70% [87]. Overtreatment is a possible negative consequence.
- Gender may have an impact on chemotherapeutic response and oncologic outcomes [261, 262]. Female patients tend to have a better cancer-related response to NAC as compared to male patients.
- Neoadjuvant chemotherapy should only be used in patients eligible for cisplatin-combination chemotherapy; other combinations (or monotherapies) are inferior in metastatic BC and have not been fully tested in a neoadjuvant setting [263-270].

7.1.2.1 Summary of available data

Several phase III RCTs addressed the potential survival benefit of NAC administration [263-267, 271-274]. The main differences in trial designs were the type of chemotherapy (i.e., single-agent cisplatin or combination chemotherapy) and the number of cycles provided. Patients had to be fit for cisplatin. Since these studies differed considerably for patient numbers, patient characteristics (e.g., clinical T-stages included) and the type of definitive treatment offered (cystectomy and/or RT), pooling of results was not possible.

Three meta-analyses were undertaken to establish if NAC prolongs survival [268-270]. In a meta-analysis including updated patient data from 11 randomised trials (n = 3,005), a significant survival benefit was shown in favour of NAC [270]. The most recent meta-analysis included four additional RCTs, and used the updated results from the Nordic I, Nordic II, and BA06 30894 trials including data from 427 new patients and updated information from 1,596 patients. The results of this analysis confirmed the previously published data and showed an 8% absolute improvement in survival at five years with a number needed-to-treat of 12.5 [275]. Only cisplatin-combination chemotherapy with at least one additional chemotherapeutic agent resulted in a meaningful therapeutic benefit [268, 270]; the regimens tested were methotrexate, vinblastine, adriamycin (epirubicin) plus cisplatin (MVA(E)C), cisplatin, methotrexate plus vinblastine (CMV), cisplatin plus methotrexate (CM), cisplatin plus adriamycin and cisplatin plus 5-fluorouracil (5-FU) [276].

The updated analysis of a large phase III RCT [264] with a median follow-up of eight years confirmed previous results and provided additional findings:

- 16% reduction in mortality risk;
- improvement in 10-year survival from 30% to 36% with neoadjuvant CMV;
- benefit with regard to distant metastases;
- the addition of neoadjuvant CMV provided no benefit for locoregional control and locoregional DFS, independent of the definitive treatment.

More modern chemotherapeutic regimens such as GC have shown similar pT0/pT1 rates as methotrexate, vinblastine, adriamycin plus cisplatin in retrospective series and pooled data analyses [276-279]. Modified dd-MVAC was tested in two small single-arm phase II studies demonstrating high rates of pathologic complete remission [280, 281]. Moreover, a large cross-sectional analysis showed higher rates of down-staging and pathological complete response for dd-MVAC [282].

In the GETUG/AFU V05 VESPER RCT of peri-operative chemotherapy, 500 patients were randomised to either 6 cycles of dd-MVAC once every 2 weeks vs. 4 cycles of GC once every 3 weeks prior to surgery (neoadjuvant group) or after surgery (adjuvant group) with a primary endpoint of progression-free survival (PFS) at 3 years. In 493 patients (437 neoadjuvant and 56 adjuvant), a similar pathologic response rate (ypT0N0) in patients treated with dd-MVAC 42% and GC 36% (p = 0.2) was seen. The < ypT2N0 rate was 63% and 50% in the dd-MVAC and GC patients, respectively. Organ-confined response (< ypT3N0) was observed more frequently in the dd-MVAC arm (77% vs. 63%, p = 0.001). For all patients in the trial, 3-year PFS was improved in the dd-MVAC arm, but the study did not meet its primary endpoint (3-year rate: 64% vs. 56%, HR: 0.77 [95% CI: 0.57–1.02], p = 0.066); nevertheless, the dd-MVAC arm was associated with a significantly longer time to progression (3-year rate: 69% vs. 58%, HR: 0.68 [95% CI: 0.50–0.93], p = 0.014). In the neoadjuvant group, PFS at 3 years was significantly higher in the dd-MVAC arm (66% vs. 56%, HR: 0.70 [95% CI: 0.51–0.96], p = 0.025). Dose- dense MVAC was associated with more severe asthenia and GI side effects than GC [258, 283]. In a single-center retrospective analysis in patients with MIBC, neoadjuvant accelerated MVAC was safe and efficacious irrespective of age, provided that patients were fit and deemed suitable candidates for cisplatin [284]. Another dose- dense regimen using GC was reported in two small phase II trials [285, 286]. While pathological response rates (< pT2) in the range of 45%–57% were achieved, one trial had to be closed prematurely due to high rates of severe vascular events [285]. This approach is therefore not recommended outside of clinical trials.

As an alternative to the standard dose of cisplatin-based NAC with 70 mg/m2 on day 1, split-dose modifications regimens are often used with 35 mg/m2 on days 1+8 or days 1+2. In a retrospective analysis the standard schedule was compared to a split-dose schedule in terms of complete and partial pathological response. A lower number of complete and partial response rates was seen in the split-dose group, but these results were not statistically significant [287].

Efforts aimed at improving the efficacy of NAC in MIBC are ongoing. In the double- blind, randomised, placebo-controlled, phase II NEOBLADE trial of neoadjuvant gemcitabine and cisplatin chemotherapy with nintedanib, a small molecule inhibitor that targets tyrosine kinases PDGFR, FGFR-1, and VEGFR-2, or placebo, in locally-advanced MIBC, the addition of nintedanib to chemotherapy was safe but did not improve the rate of pathological complete response [288].

There seem to be differences in the outcomes of patients treated with NAC for primary or secondary MIBC with retrospective data suggesting that patients with primary MIBC have better pathologic response rates to NAC in comparison to patients with secondary MIBC [289]. However, in the absence of prospective data, patients with secondary MIBC should be treated similarly to those presenting with primary MIBC [225].

It is unclear, if patients with non-UC histology will also benefit from NAC. A retrospective analysis demonstrated that patients with neuroendocrine tumours had improved OS and lower rates of non-organ-confined disease when receiving neoadjuvant cisplatinum/etoposide chemotherapy. In case of micropapillary differentiation, sarcomatoid differentiation and adenocarcinoma, lower rates of non-organ confined disease were found, but no statistically significant impact on OS. Patients with SCC did not benefit from NAC [290]. A 2019 systematic review showed benefit of NAC for patients with micropapillary-, plasmacytoid-, sarcomatoid-, and mixed variants but especially for patients with neuroendocrine tumours [66]. A U.S. National Cancer Database study evaluating potential associations between receipt of NAC, pathological downstaging and OS for patients with histological subtype MIBC demonstrated that NAC was associated with pathological downstaging for all MIBC histological subtypes (UC; sarcomatoid UC; micropapillary UC; SCC; neuroendocrine carcinoma; and adenocarcinoma), with improved OS for patients with UC, sarcomatoid variant UC and neuroendocrine carcinoma [291].

7.1.3 ***The role of imaging and predictive biomarkers*** *(see also section 5.2)*

Data from small imaging studies aiming to identify responders in patients treated with NAC suggest that response after two cycles of treatment is predictive of outcome. Although mpMRI has the advantage of better resolution of the bladder wall tissue planes as compared to CT, it is not ready yet for standard patient care. However, bladder mpMRI may be useful to inform on tumour stage after TURB and response to NAC [119]. So far PET/CT, MRI or DCE-MRI cannot accurately assess treatment response [292-295]. 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 [296, 297]. Therefore, reliable predictive markers to identify patients most likely to benefit from chemotherapy are needed. A study investigated how molecular subtypes impact pathological response and survival in patients receiving pre-operative cisplatin-based chemotherapy [298]. Patients with genomically unstable (GU) and urothelial-like (Uro) tumours had higher proportions of complete pathological response (16/31 [52%] and 17/54 [31%] vs. 5/24 (21%) for the basal/squamous (Ba/ Sq) subtype) following NAC and RC. Molecular subtype was independently associated with improved survival for patients with GU tumours (HR: 0.29, 95% CI: 0.11–0.79) and UroC tumours (HR: 0.37, 95% CI: 0.14–0.94) compared with Ba/Sq tumours, adjusting for clinical stage. Molecular tumour profiling might guide the use of NAC in the future but, as yet, this is not applicable in routine practice [299-301] (see Chapter 6 - Markers).

7.1.4 ***Role of neoadjuvant immunotherapy and chemo-immunotherapy***

Inhibition of PD-1/PD-L1 checkpoint has demonstrated significant benefit in patients with unresectable and metastatic BC in the second-line setting and in platinum-ineligible PD-L1+ patients as first-line treatment using different agents. Checkpoint inhibitors are increasingly tested also in the neoadjuvant setting; either as monotherapy or in combination with chemotherapy or CTLA-4 checkpoint inhibition. Data from two phase II trials have been presented with encouraging results [241, 242]. The results of PURE-01, a phase II trial using the PD-1 inhibitor pembrolizumab reported a complete pathological remission (pT0) in 42% and pathological response (< pT2) in 54% of patients, whereas in the single-arm phase II trial with atezolizumab a pathologic complete response rate of 31% was reported. In an update to the ABACUS trial using single-agent atezolizumab, two-year DFS and OS were 68% (95% CI: 58–76) and 77% (95% CI: 68–85), respectively with two-year DFS in patients achieving a pathological complete response of 85% (95% CI: 65–94) [302]. In a update of PURE-01, after a median follow-up of 39 months, 36-month EFS and OS were 74% (95% CI: 68-82) and 84% (95% CI: 78-90), respectively with RFS in patients achieving a complete pathologic response of 96% (95% CI: 89-100) [303]. The combination of anti-CTLA4 and anti-PD1 therapy has also been investigated in the neoadjuvant setting. In the NABUCCO study using pre-operative ipilimumab and nivolumab, the pathologic complete response was 46% with 58% having no remaining invasive disease (pT0N0/pTisN0/pTaN0) [304]. In a second study using pre-operative tremelimumab and durvalumab in cisplatin-ineligible patients, the pathological complete response was 37.5% and downstaging to pT1 or less was seen in 58% of patients who completed surgery [305].

Three studies have been published to date investigating the use of neoadjuvant chemo-immunotherapy in patients with MIBC. In a phase II study of gemcitabine plus split-dose cisplatin and pembrolizumab in patients with MIBC, 22 of 39 patients (56% [95% CI: 40–72]) achieved < pT2N0 and 14 of 39 (36% [95% CI: 21–53]) achieved pT0N0 [306]. In a second phase II study evaluating neoadjuvant atezolizumab with gemcitabine and cisplatin; 27 of 39 patients (69%) were < pT2N0 and 16 (41%) pT0N0. No patient with < pT2N0 relapsed and four (11%) with ≥ pT2N0 relapsed with a median follow-up of 16.5 months (range: 7.0–33.7 months) [307]. A third phase II study evaluating NAC with GC plus durvalumab including adjuvant durvalumab with a primary endpoint of EFS demonstrated EFS at 3 years of 73% (95% CI, 59 to 83). Complete pathologic response was achieved in 17 of 52 patients (33%), and 31 (60%) had pathologic response <ypT2 ypN0. Overall survival (OS) was 81% (95% CI, 67 to 89) at 3 years. With the promising pathologic response rates, several larger studies are currently investigating the potential role for neoadjuvant chemo-immunotherapy in patients with MIBC [308].

At present, the results with immunotherapy alone, or in combination with chemotherapy, are promising but not yet approved in routine practice.

7.1.5 Summary of evidence and guidelines for neoadjuvant therapy

Summary of evidence	LE
Neoadjuvant cisplatin-containing combination chemotherapy improves OS (8% at five years).	1a
Neoadjuvant treatment may have a major impact on OS in patients who achieve ypT0 or ≤ ypT2.	2a
Currently immunotherapy with checkpoint inhibitors as monotherapy, or in different combinations with or without chemotherapy, is being tested in phase II and III trials. Initial results are promising.	-
There are still no reliable tools available to select patients who have a higher probability of benefitting from NAC. In the future, genetic markers in a personalised medicine setting might facilitate the selection of patients for NAC and differentiate responders from non-responders.	-

Recommendations	Strength rating
If eligible for cisplatin-based chemotherapy, offer neoadjuvant cisplatin-based combination chemotherapy to patients with muscle-invasive bladder cancer (T2-T4a, cN0 M0).	Strong
Do not offer NAC to patients who are ineligible for cisplatin-based combination chemotherapy.	Strong
Only offer neoadjuvant immunotherapy to patients within a clinical trial setting.	Strong

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

7.2.1 Post-operative radiotherapy

Given the high rates of local-regional failure after RC in patients with locally-advanced (pT3–4) BC, estimated at ~30%, as well as the high risk of distant failure and poor survival for these patients, there is an interest in adjuvant therapies that address both the risk of local and distant disease. Data on adjuvant RT after RC are limited and further prospective studies are needed, but a more recent phase II trial compared adjuvant sequential chemotherapy and radiation vs. adjuvant chemotherapy alone in 120 patients with locally-advanced disease and negative margins after RC (with one or more risk factors: ≥ pT3b, grade 3, or node-positive), in a study population with 53% UC and 47% SCC. Addition of adjuvant RT to chemotherapy alone was associated with a statistically significant improvement in local relapse-free survival (at 2 years 96% vs. 69% favouring the addition of RT). Disease-free survival and OS also favoured the addition of RT, but those differences were not statistically significant and the study was not powered for those endpoints. Late-grade ≥ 3 GI toxicity in the chemoradiation arm was low (7% of patients) [309].

A 2019 systematic review evaluating the efficacy of adjuvant radiation for BC or UTUC found no clear benefit of adjuvant radiation following radical surgery (e.g., cystectomy), although the combination of adjuvant radiation with chemotherapy may be beneficial in locally-advanced disease [310].

Adjuvant radiation might be considered in patients with pT3/pT4 pN0–2 urothelial BC following RC, although this approach has been evaluated in only a limited number of studies without conclusive data demonstrating improvements in OS. Radiation fields should encompass areas at risk for harbouring residual microscopic disease based on pathologic findings at surgery and may include the cystectomy bed and pelvic LNs. Doses in the range of 45 to 50.4 Gy may be considered. A phase II trial with 72 patients showed that a dose of 50.4 of radiotherapy Gy can be used with acceptable toxicity and a high rate of local control [311]. A small retrospective study of 25 patients (median age 64 years) evaluated acute and late toxicity of moderate doses of pelvic RT (range, 45–50.4 Gy). After a median follow-up of 10.4 months the authors concluded that orthotopic ileal neobladders can tolerate moderate radiation doses without significant induced morbidity. Most of the acute GI toxicity seen was grade 1, four patients developed acute grade 2 toxicity; three of whom had been treated by NAC [312]. For patients not treated with NAC, it may be reasonable to sandwich adjuvant radiation between cycles of adjuvant chemotherapy. The safety and efficacy of concurrent radiosensitising chemotherapy in the adjuvant setting needs further study.

7.2.2 Pre-operative radiotherapy

To date, six RCTs have been published 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, resulting in a significant increase in pathological complete response (9% to 34%) in favour of pre-operative RT, which was also a prognostic factor for survival [313]. The OS data were difficult to interpret since chemotherapy was used in a subset of patients only and more than 50% of patients (241/475) did not receive the planned treatment and were excluded from the final analyses. Two smaller studies using a dose of 20 Gy showed only a small survival advantage

in ≥ T3 tumours [314, 315]. Two other small trials confirmed downstaging after pre-operative RT [316, 317]. In a retrospective analysis of 1,846 evaluable patients, only 34 patients received RT prior to orthotopic neobladder reconstruction. The authors conclude that following pelvic RT, a neobladder is possible in highly selected patients with statistically similar peri-operative complication rates compared to patients who did not receive prior RT. Patient selection, with oncologic factors (positive urethral margins, nodal involvement, and extravascular disease) more commonly than technical factors (adhesions/difficult dissection, bleeding, urethral stricture) influencing conversion from a planned neobladder reconstruction [318].

A meta-analysis of five RCTs showed a difference in 5-year survival (OR: 0.71, 95% CI: 0.48–1.06) in favour of pre-operative RT [319]. However, the meta-analysis was potentially biased by data from the largest trial in which patients were not given the planned treatment. When the largest trial was excluded from the analysis, the OR became 0.94 (95% CI: 0.57–1.55), which was not significant.

A more recent RCT, comparing pre-operative vs. post-operative RT and RC (n = 100), showed comparable OS, DFS and complication rates [320]. Approximately half of these patients had UC, while the other half had SCC. In general, such older data is limited in being able to provide a robust evidence base for modern guideline recommendations.

7.2.3 Local therapy (surgery or radiotherapy) in oligometastatic disease

The other disease state for which there may be an emerging role for adding local therapy Is oligometastatic bladder cancer. Oligometastatic status is defined as a situation with a limited number of metastatic sites. In a recent consensus, a maximum of three metastatic sites, all either resectable or amenable to stereotactic therapy, was proposed as the definition of oligometastatic bladder cancer [321]. Studies from other tumour types (prostate cancer, colorectal cancer and lung cancer) suggest possible survival benefit when adding local therapy. In bladder cancer, some retrospective studies suggest a potential survival benefit when incorporating local therapy to the bladder (including radiation therapy over chemotherapy alone) in metastatic disease [322, 323], and when employing metastasis-directed therapy. [324-327] A favourable response to systemic treatment was proposed as the criterion for selection of patients for any metastasis-directed therapy [321]. However, the data in oligometastatic disease are limited and further prospective study in bladder cancer patients is needed.

7.2.4 Summary of evidence and guidelines for pre- and post-operative radiotherapy

Summary of evidence	LE
No contemporary data exists to support that pre-operative RT for operable MIBC increases survival.	2a
Pre-operative RT for operable MIBC, using a dose of 45–50 Gy in fractions of 1.8–2 Gy, results in down-staging after 4 to 6 weeks.	2
Limited evidence supports the safe use of pre- and post-operative RT in case a neobladder is planned or *in situ*.	3
Limited high-quality evidence supports the use of pre-operative RT to decrease local recurrence of MIBC after RC.	3
Addition of adjuvant RT to chemotherapy is associated with an improvement in local relapse-free survival following cystectomy for locally-advanced bladder cancer (pT3b–4, or node-positive).	2a
There are no randomised trials showing an effect for local therapy in oligometastastic bladder cancer.	1
Retrospective case series show some survival benefit for the additional of local therapy (to the primary and to sites of metastases) in oligometastatic bladder cancer.	3

Recommendations	Strength rating
Do not offer pre-operative radiotherapy (RT) for operable muscle-invasive bladder cancer since it will only result in down-staging, but will not improve survival.	Strong
Do not offer pre-operative RT when subsequent radical cystectomy (RC) with urinary diversion is planned.	Strong
Consider offering adjuvant RT in addition to chemotherapy following RC, based on pathologic risk (pT3b–4 or positive nodes or positive margins).	Weak
Inform patients with oligometastatic disease about local therapy treatment options. Patients should be carefully selected for treatment and fully informed of the potential benefits and harms of the different treatment modalities as well as the fact that there is no definitive evidence supporting local therapy inoligometastatic disease.	Weak

7.3 Radical surgery and urinary diversion

*7.3.1 **Removal of the tumour-bearing bladder***

7.3.1.1 Introduction

For decades, the standard treatment for patients with MIBC consisted of RC, pelvic LN dissection, and urinary diversion, with or without NAC [603]. However, an increasing focus on quality of life contributes to a growing trend to use bladder-sparing approaches such as RT or TMT in selected patients (see section 7.5). A multi-institutional propensity score matched and weighted analysis showed comparable oncological outcomes between radical cystectomy and TMT for selected MIBC patients [328]. Performance status and life expectancy obviously influence the choice of primary treatment, as does the type of urinary diversion, with RC being reserved for patients with longer life expectancy without concomitant disease and better PS.

7.3.1.2 Radical cystectomy: timing

A meta-analysis including 19 studies concluded that a delay of > 3 months has a negative effect on OS (HR: 134, 95% CI: 1.18–1.53). Authors highlighted the lack of standardisation regarding the definition of delays which made it impossible to identify a clear cut-off time [329]. Overall conclusion was that BC patients scheduled for RC should be treated without delays to maximise survival.

*7.3.2 **Radical cystectomy: indications***

Radical cystectomy is recommended in patients with T2–T4a, N0M0 disease, very high-risk NMIBC, BCG-refractory, BCG-relapsing and BCG-unresponsive NMIBC (see EAU Guidelines on Non-muscle-invasive Bladder Cancer [2]), as well as extensive papillary disease that cannot be controlled with TURBT and intravesical chemotherapy/immunotherapy alone.

Salvage cystectomy is indicated in non-responders to conservative therapy, i.e., recurrence after bladder-sparing treatment. It is also used as a purely palliative intervention, including for fistula formation, pain and recurrent uncontrollable haematuria (see Section 7.4.1 - Palliative cystectomy).

*7.3.3 **Radical cystectomy: technique and extent***

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.

7.3.3.1 Radical cystectomy in men

In men, standard RC includes removal of the bladder, prostate, seminal vesicles, distal ureters, and regional LNs.

7.3.3.1.1 Concomitant prostate cancer

A systematic review and meta-analysis of 13,140 patients showed an incidental prostate cancer rate of 24% [330]. Incidental prostate cancer was associated with higher age and lower 5-year OS. However, the lower OS can be explained by the higher age of patients with incidental prostate cancer. Pathological reporting of the specimens should follow the recommendations as presented in the EAU-EANM-ESTRO-ESUR-ISUP-SIOG Guidelines on Prostate Cancer [331].

7.3.3.1.2 Sexual-preserving techniques

Four main types have been described:

1. **Prostate sparing cystectomy:** part of 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 the 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.

The systematic review on oncological and functional outcomes of sexual function-preserving cystectomy in men indentified 12 studies (n = 1,098) [332]. In the majority of cases, an open surgical approach was used and the urinary diversion of choice was an orthotopic neobladder. Median follow-up was longer than three years in nine studies, with three studies presenting results with a median follow-up longer than five years.

The majority of the studies included patients who were potent pre-operatively with organ-confined disease without tumour in the bladder neck and/or prostatic urethra. Prostate cancer was ruled out in all of the sexual-preserving cystectomy (SPC) techniques, except in the nerve-sparing approach [331].

Oncological outcomes did not differ between groups in any of the comparative studies that measured local recurrence, metastatic recurrence, DSS and OS, at a median follow-up of three to five years.

For techniques preserving prostatic tissue (prostate- or capsule-sparing), rates of incidental prostate cancer in the intervention group ranged from 0–15%. Incidental prostate cancer with ISUP grade ≥ 4 was not reported.

Post-operative potency was significantly better in patients who underwent any type of SPC technique compared to conventional RC ($p < 0.05$), ranging from 80–90%, 50–100% and 29–78% for prostate-, capsule- or nerve-sparing techniques, respectively. Urinary continence, defined as the use of 'no pads' in the majority of studies, ranged from 88–100% (day-time continence) and from 31–96% (night-time continence) in the prostate-sparing cystectomy patients. No major differences were seen with regard to continence rates between any of these approaches.

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

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

Summary of evidence	**LE**
The majority of eligible patients motivated to preserve their sexual function will benefit from sexual-preserving techniques.	2a
None of the sexual-preserving techniques (prostate/capsule/seminal/nerve-sparing) have shown to be superior, and no particular technique can be recommended.	3

Recommendations	**Strength rating**
Only offer sexual-preserving techniques to eligible men very motivated to preserve their sexual function.	Strong
Select patients based on: • organ-confined disease; • absence of any kind of tumour at the level of the prostate, prostatic urethra or bladder neck.	Strong

7.3.3.2 Radical cystectomy in women

Historically, standard RC in women includes removal of the bladder, the entire urethra and adjacent vagina, uterus, distal ureters, and regional LNs. Pelvic floor disorders, sexual and voiding dysfunction in female patients are prevalent after RC [333]. As part of the pre-operative evaluation a gynaecological history should be obtained and patients should be counselled on the potential negative impact of RC on sexual function and/ or vaginal prolapse. Most importantly, a history of cervical cancer screening, abnormal vaginal bleeding and a family history of breast and/or ovarian cancer should be recorded, as well as ruling out possible pelvic organ prolapse. Post-operatively, screening for sexual and urinary function and prolapse, is mandatory.

Pelvic organ-preserving techniques involve preserving the neurovascular bundle, vagina, uterus, ovaries or variations of any of the stated techniques. From an oncological point of view, concomitant malignancy in gynaecological organs is rare and local recurrences reported after RC are infrequent [334, 335]. In premenopausal women, by preserving ovaries, hormonal homeostasis will be preserved, decreasing risk of cognitive impairment, cardiovascular diseases and loss of bone density. In case of an increased risk of hereditary breast or ovarian cancer (i.e., BRCA1/2 mutation carriers or patients with Lynch syndrome), salpingooophorectomy should be advised after childbearing and to all women over 40 years of age [336]. On the other hand, preservation of the uterus and vagina will provide the necessary support for the neobladder, thereby reducing the risk of urinary retention. It also helps to avoid post-operative prolapse as removal of the uterus predisposes to an anterior or posterior vaginal prolapse. In case of an already existing prolapse of the uterus, either isolated or combined with a vaginal prolapse, removing the uterus will be beneficial. It is noteworthy that by resecting the vaginal wall, the vagina shortens which could impair sexual satisfaction and function.

Based on retrospective low quality data only, a systematic review evaluating the advantages and disadvantages of sexual-function preserving RC and orthotopic neobladder in female patients concluded that in well-selected patients, sparing female reproductive organs during RC appears to be oncologically safe and provides improved functional outcomes [337]. Historically, patients selection has been limited to cT2 disease, but there are recent encouraging reports that support including women with more advanced T-stage and histological subtypes without compromising oncological outcomes [338]. Nevertheless, a cross-sectional survey

of more than 100 members of the US Society of Urologic Oncology identified significant gaps in adoption of sexual preserving techniques fo rwomen with organ-confined disease; however, in 80% a non-sexual preserving technique was still applied [339].

Pelvic organ-preserving RC could be considered also in elderly and fragile patients as it may be beneficial from the point of reduced blood loss and quicker bowel recovery [340]. Nevertheless, a cross-sectional study among more than 100 members of the Society of Urologic Oncology showed that in the US a non-sex-sparing technique is still used in 80% of cases [339].

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

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

Recommendations	Strength rating
Offer sexual organ-preserving techniques to eligible women to preserve their sexual function.	Strong
Select patients based on: • absence of tumour in the area to be preserved to avoid positive soft tissue margins; • absence of pT4 urothelial carcinoma.	Strong

*7.3.4 **Lymphadenectomy: role and extent***

The optimal extent of lymphadectomy (LND) has not been established to date. Standard LND in MIBC 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. The lateral borders are the genitofemoral nerves, caudally the circumflex iliac vein, the lacunar ligament and the LN of Cloquet [341]. Limited LND includes the nodes from the true pelvis, but excluding the deep obturator nodes. Extended LND includes the same boundaries as a standard LND, except for the cranial limit which is the region of the aortic bifurcation [342]. A super-extended LND extends cranially to the level of the inferior mesenteric artery [343].

Controversies in the clinical importance of LND are related to the question whether it should be considered a staging tool, a therapeutic procedure, or both.

7.3.4.1 Diagnostic value of lymphadenectomy

To understand the lymphatic spread in MIBC, two important autopsy studies have been performed. The first study analysed 367 patients with a history of cystectomy or MIBC at the time of autopsy. In total, 215 patients (59%) had node-positive disease [344]. In these patients 92% of the positive LNs were regional (perivesical or pelvic), 72% retroperitoneal and 35% abdominal.

The second autopsy study focused on the nodal yield when super-extended pelvic LND was performed. Substantial inter-individual differences were found with counts ranging from 10 to 53 nodes [345]. These findings demonstrate the limited utility of node count as a surrogate for extent of dissection, supporting a template-based LND instead.

In addition to autopsy studies, several authors adressed the spread of lymphatic disease by performing LN mapping studies in MIBC patients undergoing RC and (super)extended PLND [346-348]. These studies have demonstrated that LN-positive disease is present in approximately 25% of patients. In the group of node-positive patients, positive LNs cranial to the iliac bifurcation were present in over 40% of patients, however, skip LN metastasis were very rare (1%), as seen in autopsy studies. From a staging perspective only, these studies suggest that a standard LND should be sufficient to identify nearly all patients with node-positive disease.

7.3.4.2 Therapeutic value of lymphadenectomy

The therapeutic value of LND is a topic of continuous debate. To assess the oncological outcomes of different LND templates, a systematic review including 19 studies was performed [349]. Five studies compared LND vs. no LND and reported better oncological outcomes for the LND group. Seven out of twelve studies comparing (super)extended with limited or standard LND reported a beneficial outcome for (super)extended LND in at least a subset of patients. Two studies did not show a difference in outcome between extended and super-extended LND [349].

The two prospective randomised trials investigating the anatomic extend of the LND are the German LEA trial and the US/Canadien SWOG S1011 trial. In the LEA trial, patients with MIBC (n = 346) or T1G3 disease (n = 55) were included. Patients underwent either a limited LND (n= 203) or extended LND (n = 198). Survival differences between the groups were seen, in favour of extended LND. However, extended LND failed to show a significant advantage (the trial was designed to show an absolute improvement of 15% in 5-year RFS by extended LND) over limited LND for RFS, CSS, and OS. The results of the SWOG S1011 trial comparing standard versus extended LND, presented at the 2023 ASCO meeting, showed in patients with clinically localised bladder cancer after a median six years follow-up no DFS (HR 1.10 [95%CI 0.87-1.42] p=0.4) or OS (HR 1.15 [95%CI 0.89-1,48] p=0.29) benefit for an extended LND. It does, however, increase the risk of side effects and post-operative mortality.

In conclusion, based on these two RCT's, an extended LND, is not associated with improved survival and increases the risk of morbidity.

7.3.5 ***Robotic-assisted laparoscopic cystectomy***

A 2019 Cochrane SR of five RCTs compared robotic radical cystectomy (RARC) with extacorporeal urinary diversion and open radical cystectomy (ORC) [350]. One study included an laparoscopic radical cystectomy arm (LRC) [351]. No differences were found in complications, time to recurrence, QoL and surgical margin rate for RARC and ORC. RARC was associated with lower transfusion rate and shorter length of hospital stay (median 0.7 days). The study had very-low to moderate certainty of evidence.

In 2023, an updated SR and meta-analysis was published including eight RCTs of which three studies performed intracorporeal urinary diversion [352]. The ERAS pathway was adopted in one study with extracorporeal urinary diversion and in three studies with intracorporeal urinary diversion [351, 353-355]. The following outcomes were reported:

- Longer length of hospital stay for ORC (0.2 days); however, differences were seen depending on geographical location. In four USA and two UK trials longer hospital stay for ORC was reported (0.6 and 1.5 days, respectively) whilst in two EU based trials longer hospital stay for RARC was reported (0.9 days).
- Higher venous trombo-events (OR 1.8) and transfusion rates (0.5 blood units) for ORC.
- Longer operative time for RARC (mean difference: 76 min).
- No differences in 90-day complication rate and post-operative ileus rate.
- No differences in positive surgical margin rate.
- No differences in QoL except for the domain of phsyical functioning favouring RARC.
- No differences in OS and RFS (median follow-up time: 36 months).

It should be noted that the meta-analysis did not distinguish between intracorporeal and extracorporeal approaches for urinary diversion in the RARC group.

Long-term oncological outcomes were also reported in a large (n = 595) single-centre study with a median follow-up of over five years. In this study comparable recurrence and survival data, including atypical recurrences (defined as one or a combination of the following: portsite metastasis or peritoneal carcinomatosis) [356]. Interrestingly, another study detected residual cancer cells in pelvic washing specimens during or after, but not before, RARC in approximately half of the patients (9/17), which was associated with aggressive histological subtypes and cancer recurrence; however, these findings requirer confirmation in larger studies [357].

An economic evaluation (healthcare and societal perspective) of a Dutch prospective multi-centre comparative effectiveness study asessing ORC (n = 168) vs. RARC (n = 180) showed that both mean healthcare costs and societal costs per patient were significantly higher after RARC, resulting in an increase in QALYs of 0.02 [358].

Data on post-RC uretero-enteric stricture rates for both ORC and RARC remain inconclusive. Results are mainly reported by high-volume centres or derive from population-based studies with a large variety of endpoints and poor controlling of potential confounders, making comparison difficult [359-363]. Especially those managed by extracorporeal diversion (RARC-ECUD) tend to have more strictures compared to intracorporeal diversion (RARC-ICUD) [363]. This is explained by the need for more extensive dissection of ureter in RARC-ECUD, more tension, resulting in impaired blood supply [364, 365].

7.3.5.1 Summary of evidence and guidelines for robotic-assisted laparoscopic cystectomy

Summary of evidence	LE
Robot-assisted radical cystectomy (RARC) and open radical cystectomy (ORC) provide similar 90-day complication rates, surgical margin rates, median-term oncological outcomes and quality of life outcome.	1a
Operative time is longer for RARC compared to ORC (1 to 1.5 hours), but with less blood loss and possibly shorter length of hospital stay compared to ORC.	1a
Surgeons experience and institutional volume are considered the key factor for outcome of both RARC and ORC, not the technique.	4

Recommendations	Strength rating
Inform the patient of the advantages and disadvantages of open radical cystectomy (ORC) and robot-assisted radical cystectomy (RARC) to allow selection of the proper procedure.	Strong
Select experienced centres, not specific techniques, both for RARC and ORC.	Strong

*7.3.6 **Urinary diversion after radical cystectomy***

Different types of segments of the intestinal tract can be used to reconstruct the urinary tract, including the ileum, colon and appendix, with ileum used in most cases. Several studies have compared advantages and disadvantages in terms of QoL, sexual function, urinary continence and body image between different urinary diversions [366], but further research evaluating the impact of tumour stage, functional- and socio-economic status are needed.

7.3.6.1 Different types of urinary diversion

For the choice of urinary diversion, comorbidity, cardiac, pulmonary and cognitive function are important factors that should be considered, along with the patient's social support and preference (see Section patient selection/ comorbidities). 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 [367]. Randomised controlled trials comparing conduit diversion with neobladder or continent cutaneous diversion have not been performed.

7.3.6.1.1 Uretero-cutaneostomy

Ureteral diversion to the abdominal wall is the simplest form of cutaneous diversion. Operating time, complication rate, blood loss, transfusion rate, stay at intensive care and length of hospital stay are lower in patients treated with ureterocutaneostomy as compared to ileal conduit [368]. In frail patients and/or in those with a solitary kidney who need a supravesical diversion, uretero-cutaneostomy is the preferred procedure. In case patients have both kidneys and need a uretero-cutaneostomy, either one ureter, to which the other shorter one is attached end-to-side, is connected to the skin (trans-uretero-cutaneostomy) or both ureters may be directly anastomosed to the abdominal wall creating a stoma.

Due to the smaller diameter of the ureters, stoma stenosis and ascending UTIs have been observed more frequently for this technique as compared to using small or large bowel to create an intestinal stoma [369].

7.3.6.1.2 Ileal conduit

The ileal conduit is an established option with well-known/predictable results. Early complications (30-day cut off, used in most publications) include UTIs, pyelonephritis, ureteroileal leakage and stenosis which occur in 48% of patients [370].

7.3.6.1.3 Orthotopic neobladder

According to Dutch-, German- and Spanish bladder cancer registry data, an orthotopic bladder substitution to the urethra is used in approximately 10–20% of both male and female patients. Emptying of the reservoir anastomosed to the urethra requires abdominal straining, and sphincter relaxation. The terminal ileum is the GI segment most often used for orthotopic bladder substitution. Early and late morbidity in up to 22% of patients is reported [371].

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 [372, 373]. According to the long-term results, the UUT is protected sufficiently by either method [371].

A study comparing cancer control and patterns of disease recurrence in patients with neobladder and ileal conduit showed no difference in CSS between the two groups when adjusting for pathological stage [374]. Urethral recurrence in neobladder patients seems rare (0.8–13.7% [pooled estimate of 4.6% in both male and female patients, also considering the significantly higher recurrence rates in male patients]) [375]. These results indicate that neobladder in male and female patients does not compromise the oncological outcome of cystectomy.

7.3.6.1.4 Continent cutaneous urinary diversion

Continent cutaneous urinary diversion (a low-pressure detubularised ileal reservoir for self-catheterisation) and uretero-rectosigmoidostomy are rarely used techniques nowadays, due to their high complication rates, including stomal stenosis, incontinence in the continent cutaneous diversion, UUT infections and stone formation in case of uretero-rectosigmoidostomy [376].

7.3.6.2 Patient selection

Ensuring that patients make a well-informed decision about the type of urinary diversion is associated with less decision regret post-operatively, independent of the method selected [377]. Therefore, all applicable forms of urinary diversion should be discussed, taking into account patient preference, comorbidities, age and tumour characteristics.

Diagnosis of an invasive urethral tumour prior to cystectomy leads to urethrectomy which is a contraindication for a neobladder reconstruction. Non-muscle-invasive BC in prostatic urethra or bladder neck biopsies does not necessarily preclude orthotopic neobladder substitution, provided that patients undergo regular follow-up cystoscopy and urinary cytology [378]. In women undergoing RC the rate of concomitant urethral malignancy has been reported to range from 12–16% [379]. Localisation of the primary tumour at the bladder neck correlated strongly with concomitant urethral malignancy. Bladder neck biopsies prior to RC are important in women scheduled for an orthotopic bladder substitute [380].

In the presence of positive LNs, orthotopic neobladder can be considered in case of N1 disease, but not in N2 or N3 tumours [381].

Oncological results after orthotopic neobladder or illial conduit are similar in terms of local or distant metastasis recurrence, but secondary urethral tumours seem less common in patients with a neobladder compared to those with conduits or continent cutaneous diversions [382].

Patients undergoing continent urinary diversion must be motivated to learn about their diversion and to be manually skilful to be able to deal with their diversion. Contraindications to continent urinary diversions include:

- debilitating neurological and psychiatric illnesses;
- limited life expectancy;
- severe impaired liver or renal function.

Relative contraindications for an orthotopic neobladder are high-dose pre-operative RT, complex urethral strictures and severe urethral sphincter-related incontinence [383].

A retrospective study including 1,383 patients showed that the risk of a decline in estimated glomerular filtration rate (eGFR) did not significantly differ after ileal conduit vs. neobladder in patients with pre-operative chronic kidney disease 2 (eGFR 60–89 mL/min/1.73 m2) or 3a (eGFR 45–59 mL/min/1.73 m2) [384]. Only age and anastomotic strictures were found to be associated with a decline in eGFR.

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. In selected patients, such as patients with a single kidney, uretero-cutaneostomy is surgically the least burdensome type of diversion. Recommendations related to RC and urinary diversions are listed in Section 7.3.10.

7.3.6.3 Peri-operative care

Similar to other tumour types, such as colorectal cancer, the application of a multimodal prehabilitation programme (i.e. physiotherapy, nutritional intervention, cessation of smoking) may improve patient health status prior to surgery and subsequently reduce postoperative complication rates [385]. However, evidence on this is limited and randomised controlled trials are missing.

Patients treated according to a 'Fast track'/ERAS (Early Recovery After Surgery) protocol have shown to score better on the emotional and physical functioning scores and suffer less from wound healing disorders, fever and thrombosis [386].

Pre-operatively, the ERAS protocol recommends no bowel prepation or fasting. Other components are, for example, same day admission, as well as carbohydrate loading and a pre-operative exercise programme.

Important post-operative components of the ERAS protocol are pain management, which involves reducing the use of opioids; increasing the use of high-dose acetaminophen and/or ketorolacs (only as breakthrough pain medication) and patients on ERAS experience more pain as compared to patients on a traditional protocol (Visual Analogue Scale [VAS] 3.1 vs. 1.1, $p < 0.001$), but post-operative ileus decreased from 22% to 7.3% ($p = 0.003$) [387].

Venous thromboembolism (VTE) prophylaxis may be implemented as part of an ERAS protocol. A single- centre non-randomised study showed a significant lower 30-day VTE incidence rate in patients treated for 28 days with enoxaparin compared to patients without prophylaxis [388]. Data from the Ontario Cancer Registry including 4,205 cystectomy patients of whom 1,084 received NAC showed that VTE rates are higher in patients treated with NAC as compared to patients treated with cystectomy only (12% vs. 8%, $p = 0.002$) [389].

7.3.7 ***Morbidity and mortality***

In four retrospective studies and one population-based cohort study, the peri-operative mortality after RC was reported as 2.1–3.2% at 30 days and 3.4–8.0% at 90 days [390, 391]. Morbidity rates differ strongly according to the reporting system used. Using the Clavien-Dindo Classification system complication rates ranged from 50–88% (I–IV) and severe complications from 30–42% (≥ III) [392-395]. In large national databases and institutional series, readmission rates are approximately 25% within 30 days of discharge [396]. Late morbidity was usually linked to the type of urinary diversion (see also above). 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 [397, 398]. 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 [399-402]. A retrospective analysis of 1,303 patients managed in 7 (non-academic) Dutch hospitals revealed variation in treatment preferences between them; however, despite this there was no significant difference in overall survival [403].

Table 7.1: Management of neobladder morbidity (30-64%) [404]

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, analgesics, 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 day 1) Chewing gum Avoid fluid excess and hypovolemia (provoke splanchnic hypoperfusion)
		Post-operative nausea and vomiting	Antiemetic agent (decrease opioids) Nasogastric intubation
		Urinary infection	Antibiotics, no ureteral catheter removal Check the 3 drainages (ureters and neobladdder)
		Ureteral catheter obstruction	Inject 5 cc saline in the ureteral catheter to resolve the obstruction Increase volume infusion to increase diuresis
		Intra-abdominal urine leakage (anastomosis leakage)	Check and reposition drainages, if needed
		Anaemia well tolerated	Martial treatment (give iron supplement)
		Late complications:	
		Non-compressive lymphocele	Watchful waiting
		Mucus cork	Catheterise and rinse the bladder
		Incontinence	Urine analysis (infection), echography (post-void residual) Physiotherapy
		Retention	Drainage and self-catheterisation education
		Ureteral reflux	No treatment if asymptomatic
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[1]
		Pulmonary embolism	Heparinotherapy[2]
		Pyelonephritis	Antibiotics and check kidney drainage (nephrostomy if necessary)
		Confusion or neurological disorder	Neuroleptics and avoid opioids
Grade III	Requiring surgical, endoscopic or radiological intervention	Ureteral catheter accidentally dislodged	Reposition the ureteral catheter
		Anastomosis stenosis (7%)	Renal drainage (ureteral catheter or nephrostomy)
III-a	Intervention not under general anaesthesia	Compressive lymphocele	Transcutaneous drainage

III-b	Intervention under general anaesthesia	Ileal anastomosis leakage	Ileostomy, as soon as possible
		Evisceration	Surgery in emergency
		Compressive lymphocele	Surgery (marsupialisation)
Grade IV	Life-threatening complication (including central nervous system complications: brain haemorrhage, ischaemic stroke, subarachnoid bleeding, but excluding transient ischaemic attacks) requiring intensive care/ intensive care unit management.	Neobladder rupture	Nephrostomy and indwelling catheter/surgery for draining the neobladder
		Severe sepsis	Antibiotics and check all the urinary drainages and CT scan in emergency
IV-a	Single organ dysfunction	Non-obstructive renal failure	Bicarbonate/aetiology treatment (including dialysis)
IV-b	Multi-organ dysfunction	Obstructive pyelonephritis and septicaemia	Treatment at intensive care unit, including urinary drainage and antibiotics
Grade V	Death of a patient		
Suffix 'd'	*If the patient suffers from a complication at the time of discharge, the suffix "d" (for 'disability') is added to the respective grade of complication. This label indicates the need for a follow-up to fully evaluate the complication.*		

[1] *A systematic review showed that peri-operative blood transfusion (PBT) in patients who undergo RC correlates with increased overall mortality, CSM and cancer recurrence. The authors hypothesised that this may be caused by the suggested immunosuppressive effect of PBT. In a retrospective study, Buchner and co-workers showed 5-year decreased CSS in cases where intra-operative blood transfusion (CSS decreased from 67% to 48%) or post-operative blood transfusion (CSS decreased from 63% to 48%) were given [405].*

[2] *Hammond and co-workers reviewed 20,762 cases of VTE after major surgery and found cystectomy patients to have the second-highest rate of VTE among all cancers studied [406]. These patients benefit from 30 days low-molecular-weight heparin prophylaxis. Subsequently, it was demonstrated that BMI > 30 and non-urothelial BCs are independently associated with VTE after cystectomy. In these patients extended (90 days) heparin prophylaxis should be considered [389].*

7.3.8 ***Survival***

Of all cancers, bladder cancer ranks 13th in terms of mortality, with rates decreasing particularly in the most developed countries [407].

Disease-free survival and OS in a large population-based study was 35% and 58% at ten years, respectively [408]. However, the 5-year OS in node-positive patients who underwent cystectomy was 18% [409].

A systematic review including 57 studies (n = 30,293) assessed the long-term survical of patients treated with trimodality therapy (TMT) and RC [408]. Ten-year OS was 30.9% and 35.1%, for TMT and RC, respectively with a mean DSS of 50.9% for TMT and 57.8% for RC. For T2 disease, 10-year DSS was 69% and 78.9% for TMT and RC, respectively and for T3/T4 disease 43.5% and 43.1% for TMT and RC, respectively. Three percent of the patients (812 of 27,867) received NAC, resulting in 5-year OS and DSS in downstaged patients (≤ pT1) at RC of 75.7% and 88.3%, respectively.

7.3.9 ***Impact of hospital and surgeon volume on treatment outcomes***

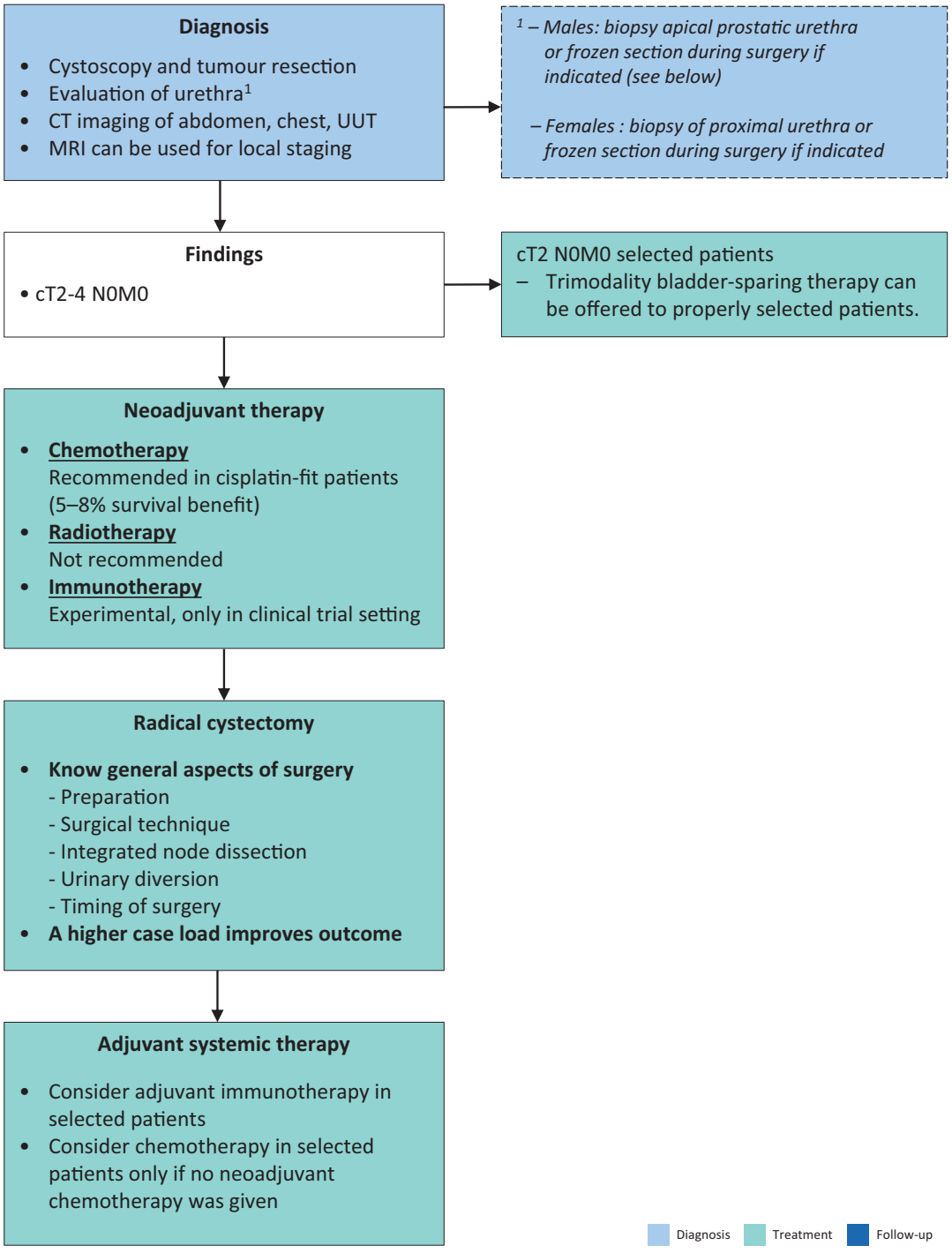
In a systematic review including 40 retrospective studies with 56,000 patients, the impact of hospital and/ or surgeon volume and peri-operative outcomes of RC was assessed [410]. A higher hospital volume was associated with lower in-hospital, 30-day and 90-day mortality. In addition, higher volume hospitals were more likely to have lower positive surgical margins, higher number of LNDs and neobladders and lower complication rates. For surgeon volume, less evidence was available. This study suggested performing at least 10 RCs per centre annually and preferably more than 20. Recently, a nationwide analysis of the Dutch Cancer Registry including almost 9,500 patients between 2008 and 2018 reported decreased 30- and 90-day mortality rates for annual hospital volumes of > 30 RCs. Furthermore, this study showed no true plateau curve for 30- and 90-day mortality beyond 30 RCs supporting the 'more is better' principle [411, 412].

7.3.10 *Summary of evidence and guidelines for radical cystectomy and urinary diversion*

Summary of evidence	LE
Higher RC hospital volume is associated with lower post-operative mortality rates and higher quality of care.	3
Radical cystectomy includes removal of regional LNs.	3
There are data to support that extended vs. standard LND improves survival after RC.	3
No conclusive evidence exists as to the optimal extent of LND.	2a
Ensuring that patients are well informed about the various urinary diversion options prior to making a decision may help prevent or reduce decision regret, independent of the method of diversion selected.	3
The type of urinary diversion does not affect oncological outcome.	3
The use of extended VTE prophylaxis significantly decreases the incidence of VTE after RC.	3
In patients aged > 80 years with MIBC, cystectomy is an option.	3
Surgical complications of cystectomy and urinary diversion should be reported using a uniform grading system. Currently, the best-adapted grading system for cystectomy is the Clavien Dindo grading system.	2b

Recommendations	Strength rating
Do not delay radical cystectomy (RC) for > 3 months as it increases the risk of progression and cancer-specific mortality, unless the patient receives neoadjuvant chemotherapy.	Strong
Perform at least 10, and preferably > 20, RCs per hospital/per year.	Strong
Before RC, fully inform the patient about the benefits and potential risks of all possible alternatives. The final decision should be based on a balanced discussion between the patient and the surgeon.	Strong
Do not offer an orthotopic bladder substitute diversion to patients who have an invasive tumour in the urethra or at the level of urethral dissection.	Strong
Do not offer pre-operative bowel preparation.	Strong
Employ ‘Fast track’ measurements to reduce the time to bowel recovery.	Strong
Offer pharmacological VTE prophylaxis, such as low-molecular-weight heparin to RC patients, starting the first day post-surgery, for a period of at least 4 weeks.	Strong
Offer RC to patients with T2–T4a, N0M0 disease or very high-risk non-muscle-invasive bladder cancer.	Strong
Perform a lymph node dissection as an integral part of RC.	Strong

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



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

7.4 Palliative and salvage cystectomy

Unresectable locally-advanced tumours (T4b, invading the pelvic or abdominal wall) may be accompanied by debilitating symptoms, including bleeding, pain, dysuria and urinary obstruction. These patients are candidates for palliative treatments, such as palliative RT. If control of the symptoms is not possible by less invasive methods, patients may be offered a palliative cystectomy with urinary diversion or urinary diversion only. Palliative cystectomy carries the greatest morbidity, particularly in patients with a poor PS. In a series of 74 patients who underwent palliative cystectomy, severe complications (Clavien-Dindo grade ≥ 3) occurred in 30%. The 30-day mortality rate was 9% and at eight months follow-up, 70% had died [413].

In a retrospective single-centre analysis, Pieretti et al., grouped 265 patients into salvage cystectomy post-TMT, primary cystectomy or primary cystectomy with prior history of non-TMT abdominal or pelvic RT. Post-TMT salvage cystectomy was associated with a higher incidence of any late (HR: 2.3, p = 0.02) and major late complications (HR: 2.1, p < 0.05) but there was no difference in DSS (p = 0.8) or OS (p = 0.9) between the groups [414].

*7.4.1 **Guidelines for palliative and salvage cystectomy***

Recommendations	Strength rating
Offer radical cystectomy as a palliative treatment to patients with locally-advanced tumours (T4b).	Weak
Offer palliative cystectomy to patients with symptoms if control is not possible by less invasive methods.	Weak

*7.4.1.1 EAU-ESMO consensus statements on the management of advanced- and variant bladder cancer [81, 82]**

Consensus statement
In patients with clinical T4 or clinical N+ disease (regional), radical chemoradiation can be offered accepting that this may be palliative rather than curative in outcome.
Chemoradiation should be given to improve local control in cases of inoperable locally-advanced tumours.

**Only statements which met the a priori consensus threshold across all three stakeholder groups are listed (defined as ≥ 70% agreement and ≤ 15% disagreement, or vice versa).*

*7.4.2 **Supportive care***

7.4.2.1 Obstruction of the upper urinary tract

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.

7.4.2.2 Bleeding and pain

In the case of bleeding, the patient must be screened first for coagulation disorders or the patient's use of anticoagulant drugs must be reviewed. Transurethral (laser) coagulation may be difficult in a bladder full of tumour or with a bleeding tumour. Intravesical rinsing of the bladder with 1% silver nitrate or 1–2% alum can be effective [415]. This 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 [415]. Vesicoureteral reflux should be excluded to prevent renal complications.

Radiation therapy is another common strategy to control bleeding and is also used to control pain. An older study reported control of haematuria in 59% of patients and pain control in 73% [416]. 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% [415]. Radical surgery is a last resort and includes cystectomy and diversion (see above, Section 7.4.1).

7.5 Bladder-sparing treatments for localised disease

*7.5.1 **Transurethral resection of bladder tumour***

Transurethral resection of bladder tumour alone in MIBC patients 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 [417]. In general, approximately 50% of patients will still have to undergo RC for recurrent MIBC with a disease-specific mortality rate of up to 47% in this group [418]. A disease-free status at re-staging TURB appears to be crucial in making the decision not to perform RC [419, 420]. A prospective study by Solsona *et al.*, including 133 patients after radical TURB and re-staging negative biopsies, reported a 15-year follow-up [420]. Thirty per cent of patients 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 CSS rates 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 refuses open surgery, or as part of a TMT bladder-preserving approach.

7.5.1.1 *Guideline for transurethral resection of bladder tumour*

Recommendation	Strength rating
Do not offer transurethral resection of bladder tumour alone as a curative treatment option as most patients will not benefit.	Strong

7.5.2 ***External beam radiotherapy***

Current RT techniques with soft-tissue matching and image guidance result in superior bladder coverage and a reduced integral dose to the surrounding tissues. The target total dose (to bladder and/or bladder tumour) for curative EBRT in BC is 64–66 Gy [421, 422]. A reasonable alternative is moderately hypofractionated EBRT to 55 Gy in 20 fractions which has been suggested to be non-inferior to 64 Gy in 32 fractions in terms of invasive locoregional control, OS, and late toxicity. In a phase II study, 55 patients (median age 86) with BC, unfit for cystectomy or even daily RT, were treated with 6-weekly doses of 6 Gy [423]. Forty-eight patients completed EBRT with acceptable toxicity and 17% showed local progression after two years demonstrating good local control with this more ultra-hypofractionated schedule.

Elective treatment to the LNs is optional and should take into account patient comorbidities and the risks of toxicity to adjacent critical structures. For node-positive disease, consider boosting grossly involved nodes to the highest achievable dose that does not violate normal tissue constraints based on the clinical scenario.

The use of modern standard EBRT techniques results in major related late morbidity of the urinary bladder or bowel in less than 5% of patients [424]. Acute diarrhoea is reduced even more with intensity-modulated RT [425]. Important prognostic factors for outcome include response to EBRT, tumour size, hydronephrosis, presence of CIS, and completeness of the initial TURB. Additional prognostic factors reported are age and stage [426].

With the use of modern EBRT techniques, efficacy and safety results seem to have improved over time. A 2002 Cochrane analysis demonstrated that RC has an OS benefit compared to RT [427], although this was not the case in a 2014 retrospective review using a propensity score analysis [428].

In a 2017 retrospective cohort study of U.S. National Cancer Database data, patients over 80 were identified with cT2–4, N0–3, M0 BC, who were treated with curative EBRT (60–70 Gy, n = 739) or concurrent chemoradiotherapy (n = 630) between 2004 and 2013 [429]. The 2-year OS was 42% for EBRT vs. 56% for chemoradiotherapy ($p < 0.001$). For EBRT a higher RT dose and a low stage were associated with improved OS.

In conclusion, although EBRT results seem to improve over time, EBRT alone does not seem to be as effective as surgery or TMT therapy (see Section 7.5.4). Factors that influence outcome should be considered. However, EBRT can be an alternative treatment in patients unfit for radical surgery or concurrent chemotherapy, and it can also be effective in helping control bleeding.

The results of several studies show that radiotherapy delivered in a hypofractionated regime (such as 21 Gy in 3 fractions evaluated in the MRC BA09 randomised control trial [430], can provide rapid relief of local bladder cancer symptoms, including in particular symptomatic hematuria. Other fractionation regimes include 35 Gy in 10 fractions, 30 Gy in 5 fractions, 36 Gy in 6 fractions given once weekly [431], and even a single 8 Gy fraction. In the palliative setting, symptom resolution typically lasts for the majority of the patients' remaining lifespan.

7.5.2.1 *Summary of evidence and guideline for external beam radiotherapy*

Summary of evidence	LE
External beam RT alone should only be considered as a therapeutic option when the patient is unfit for cystectomy or chemoradiation.	3
Radiotherapy can also be used to stop bleeding from the tumour when local control cannot be achieved by transurethral manipulation.	1b

Recommendation	Strength rating
Do not offer radiotherapy alone as primary therapy for localised bladder cancer.	Strong

*7.5.2.2 EAU-ESMO consensus statements on the management of advanced and variant bladder cancer [81, 82]**

Consensus statement
Radiotherapy alone (single block) is not the preferred radiotherapeutic schedule.
Radiotherapy for bladder preservation should be performed with IMRT and IGRT to reduce side effects.
Dose escalation above standard radical doses to the primary site in case of bladder preservation, either by IMRT or brachytherapy, is not recommended.

**Only statements which met the a priori consensus threshold across all three stakeholder groups are listed (defined as ≥ 70% agreement and ≤ 15% disagreement, or vice versa).*
IGRT = image-guided radiotherapy; IMRT = intensity-modulated radiotherapy.

7.5.3 Chemotherapy

Chemotherapy alone rarely produces durable complete remissions. In general, a clinical complete response rate of up to 56% is reported in some series, which must be weighed against a staging error of > 60% [432, 433]. Response to chemotherapy is a prognostic factor for treatment outcome and eventual survival although it may be confounded by patient selection [434].

Several groups have reported the effect of chemotherapy on resectable tumours (neoadjuvant approach), as well as unresectable primary tumours [263, 274, 435, 436]. Neoadjuvant chemotherapy with two to three cycles of MVAC or CMV has led to a down-staging of the primary tumour in various prospective series [263, 274, 435].

A bladder-conserving strategy with TURB and systemic cisplatin-based chemotherapy has been reported several years ago and could lead to long-term survival with intact bladder in a highly selected patient population [437].

A recent large retrospective analysis of a U.S. National Cancer Database cohort reported on 1,538 patients treated with TURB and multi-agent chemotherapy [438]. The two and 5-year OS for all patients was 49% and 32.9% and for cT2 patients it was 52.6% and 36.2%, respectively. While these data show that longterm survival with intact bladder can be achieved in a subset of patients it is not recommended for routine use.

7.5.3.1 Summary of evidence and guideline for chemotherapy

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

Recommendation	Strength rating
Do not offer chemotherapy alone as primary therapy for localised bladder cancer.	Strong

7.5.4 Trimodality bladder-preserving treatment

Bladder preservation as an alternative to RC is generally reserved for patients with smaller solitary tumours, no extensive or multifocal CIS, no tumour-related hydronephrosis, and good pre-treatment bladder function. Trimodality bladder-preserving treatment should also be considered in all patients with a contraindication for surgery, either a relative or absolute contraindication since the factors that determine fitness for surgery and chemoradiotherapy differ.

Trimodality therapy combines TURB, chemotherapy and RT. The rationale to combine TURB with RT is to achieve maximal local tumour control in the bladder and adjacent nodes. The addition of radiosensitising chemotherapy or other radiosensitisers (mentioned below) is aimed at the potentiation of RT. Micrometastases are targeted by platinum-based combination chemotherapy (for details see Section 7.1). The aim of TMT is to preserve the bladder and QoL without compromising oncological outcome. There are no definitive contemporary data supporting the benefit of using neoadjuvant or adjuvant chemotherapy combined with chemoradiation. Patient selection is critical in achieving good outcomes [439]. Whether a node dissection should be performed before TMT as in RC remains unclear [81, 82].

In the case of TMT, two distinct patterns of care emerge; treatment aimed at patients fit for cystectomy who elect TMT or refuse cystectomy, and treatment aimed at older, less fit, patients. For the former category, TMT presents selective bladder preservation and in this case the initial step is a radical TURB where as much tumour as possible should be resected. In this case appropriate patient selection (e.g., T2 tumours, no CIS) is crucial

[440, 441]. Even in case of an initial presumed complete resection, a second TUR has been suggested to reveal tumour in > 50% of patients and subsequently improves 5-year OS in case of TMT [442]. For patients who are not candidates for cystectomy, less stringent criteria can be applied, but extensive CIS and poor bladder function should both be regarded as relative contraindications.

A collaborative review has described the principles of TMT [439]. For radiation, two schedules are most commonly used; historically within the RTOG a split-course format with interval cystoscopy [443] and single-phase treatment which is now more commonly used [444]. A conventional radiation schedule includes EBRT to the bladder and limited pelvic LNs with an initial dose of 40-45 Gy, with a boost to the whole bladder of 50–54 Gy and a further tumour boost to a total dose of 60–66 Gy. If not boosting the tumour, it is also reasonable for the whole bladder to be treated to 59.4–66 Gy. For node-positive disease, consider boosting grossly involved nodes to the highest achievable dose that does not violate normal tissue constraints. Therefore, elective treatment to the LNs (when node negative) is optional and should take into account patient comorbidities and the risks of toxicity to adjacent critical structures.

A reasonable radiation dosing alternative to conventional fractionation when treating the bladder-only fields is moderately hypofractionated EBRT to 55 Gy in 20 fractions which has been suggested to be non-inferior to 64 Gy in 32 fractions in terms of invasive loco-regional control, OS and late toxicity [421, 445] in a meta-analysis of individual patient data from the BC2001 and BCON studies.

Different concurrent chemotherapy regimens have been used, but most evidence exists for cisplatin [446] and mitomycin-C plus 5-FU [444]. Alternative regimens that have been evaluated include: single agent gemcitabine [447], capecitabine [448] and hypoxia modification with carbogen/nicotinamide [81, 82]. In a recently published phase II RCT, twice-a-day radiation plus 5-FU/cisplatin was compared to once-daily radiation plus gemcitabine [447]. Both arms were found to result in a > 75% free from distant metastases rates at 3 years (78% and 84%, respectively). Therefore, there are good chemotherapy options for non-cisplatin candidates such as 5-FU/mitomycin-C or low-dose gemcitabine.

Five-year CSS and OS rates vary between 50%–84% and 36%–74%, respectively, with salvage cystectomy rates of 10–30% [439, 440, 444, 446, 449].

There are no successfully completed RCTs comparing the outcome of TMT with RC. The BC2001 trial with 10 year follow-up showed that combined radiotherapy with mitomycin C and fluorouracil significantly improved locoregional control and five year cystectomy rates and non-significantly improved DFS, OS and DSS compared to radiotherapy alone [450] as shown in other studies [443, 444, 451]. Many of the reported series have differing characteristics as compared to the larger surgical series, which typically have median ages in the mid- to-late 60s compared to mid-70s for some large RT series (reviewed by James, *et al.* [444]).

As there are no completed randomised trials, RC and TMT have been compared in systematic reviews, meta-analyses, large population-based studies and multi-institutional propensity score matched and weighted analyses [328, 408, 452]. Overall, in balance, these studies show similar oncological outcomes between radical cystectomy and trimodality therapy for select patients with muscle-invasive bladder cancer. These results support that trimodality therapy, in the setting of multidisciplinary shared decision making, should be offered to all suitable candidates with muscle-invasive bladder cancer and not only to patients with significant comorbidities for whom surgery is not an option [328].

Another study reported no difference in survival outcomes in cN+ patients treated with surgery versus radical RT [453].

The Boston group has also reported on their experience in 66 patients with mixed histological subtypes treated with TMT and found similar complete response, OS, DSS and salvage cystectomy rates as in UC [454]. The majority of recurrences post-TMT are non-invasive and can be managed conservatively [444]. In contemporary series, salvage cystectomy is required in about 10–15% of patients treated with TMT and can be curative [328, 440, 444, 449]. Current data suggest that major late complication rates are slightly higher but remain acceptable for salvage- vs. primary cystectomy [455].

A sub-analysis of two RTOG trials looked at complete response (T0) and near-complete response (Ta or Tis) after TMT [456]. After a median follow-up of 5.9 years 41/119 (35%) of patients experienced a bladder recurrence, and fourteen required salvage cystectomy. There was no difference between complete and near-complete responders. Non-muscle-invasive BC recurrences after complete response to TMT were reported in

25% of patients by the Boston group, sometimes over a decade after initial treatment [457]. A NMIBC recurrence was associated with a lower DSS, although in properly selected patients, intravesical BCG could avoid immediate salvage cystectomy.

Overall significant late pelvic (GI/genitourinary [GU]) toxicity rates after TMT are low and QoL is good [444, 458, 459]. A combined analysis of survivors from four RTOG trials with a median follow-up of 5.4 years showed that combined-modality therapy was associated with low rates of late grade 3 toxicity (5.7% GU and 1.9% GI). No late grade 4 toxicities or treatment-related deaths were recorded [458]. A retrospective study showed QoL to be good after TMT and in most domains better than after cystectomy, although prospective validations are needed [460]. One option to reduce side effects after TMT is the use of IMRT and image-guided RT (IGRT) [81, 82, 461].

A bladder-preserving TMT strategy requires very close multidisciplinary cooperation [81, 82]. This was also highlighted by a Canadian group [462]. In Ontario between 1994 and 2008 only 10% (370/3,759) of patients with cystectomy had a pre-operative radiation oncology consultation, with high geographical variations. Independent factors associated with this consultation included advanced age ($p < 0.001$), greater comorbidity ($p < 0.001$) and earlier year of diagnosis ($p < 0.001$). A bladder-preserving TMT strategy also requires a high level of patient compliance. Even if a patient has shown a clinical response to a TMT bladder-preserving strategy, the bladder remains a potential source of recurrence, hence long-term life-long bladder monitoring is essential and patients should be counselled that this will be required.

7.5.4.1 Summary of evidence and recommednations for trimodality bladder-preserving treatment

Summary of evidence	**LE**
Long-term survival rates of TMT bladder-preserving treatment are comparable to those of early cystectomy . The contraindications for TMT or surgery have to be considered.	2
Combined chemotherapy and radiotherapy is more effective than radiotherapy alone in bladder sparing treatment.	1b

Recommendations	**Strength rating**
Offer surgical intervention or trimodality bladder-preserving treatments (TMT) to appropriate candidates as primary curative therapeutic approaches since they are more effective than radiotherapy alone.	Strong
Advise patients who are candidates for TMT in a mutlidisciplinary setting including urologists, medical oncologists and radiation oncologists concerning the benfits and harms of TMT.	Strong
Offer TMT as an alternative to selected, well-informed and compliant patients, especially for whom radical cystectomy is not an option or not acceptable.	Strong
Advise patients who are candidates for TMT that life-long bladder monitoring is essential.	Strong

*7.5.4.2 EAU-ESMO consensus statements on the management of advanced- and variant bladder cancer [81, 82]**

Consensus statement
Candidates for curative treatment, such as cystectomy or bladder preservation, should be clinically assessed by at least an oncologist, a urologist, a radiation oncologist (in case adjuvant radiotherapy or bladder preservation is considered) and a neutral HCP such as a specialist nurse.
An important determinant for patient eligibility in case of bladder-preserving treatment is absence of carcinoma *in situ*.
An important determinant for patient eligibility in case of bladder-preserving treatment is absence or presence of hydronephrosis.
When assessing patient eligibility for bladder preservation, the likelihood of successful debulking surgery should be taken into consideration (optimal debulking).
In case of bladder preservation with radiotherapy, combination with a radiosensitiser is always recommended to improve clinical outcomes, such as cisplatin, 5-FU/MMC, carbogen/nicotinamide or gemcitabine.
Radiotherapy for bladder preservation should be performed with IMRT and IGRT to reduce side effects.
Dose escalation above standard radical doses to the primary site in case of bladder preservation, either by IMRT or by brachytherapy, is not recommended.

**Only statements which met the a priori consensus threshold across all three stakeholder groups are listed*

(defined as ≥ 70% agreement and ≤ 15% disagreement, or vice versa).
HCP = healthcare professional; IGRT = image-guided radiotherapy; IMRT = intensity-modulated radiotherapy; 5FU = 5-fluorouracil; MMC = mitomycin-C.

7.6 Adjuvant therapy

7.6.1 Role of adjuvant platinum-based chemotherapy

Adjuvant chemotherapy after RC for patients with pT3/4 and/or LN positive (N+) disease without clinically detectable metastases (M0) is still under debate. 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 of or intolerability to chemotherapy, due to post-operative morbidity [463].

There is limited evidence from adequately conducted and accrued phase III RCTs in favour of the routine use of adjuvant chemotherapy [464-469]. An individual patient data meta-analysis [470] of survival data from six RCTs of adjuvant chemotherapy [471-473] included 491 patients (unpublished data from Otto *et al.*, were included in the analysis). All included trials suffered from significant methodological flaws including small sample size (underpowered), incomplete accrual, use of inadequate statistical methods and design flaws (irrelevant endpoints and failing to address salvage chemotherapy in case of relapse or metastases) [464]. In these trials, three or four cycles of CMV, cisplatin, cyclophosphamide, and adriamycin (CISCA), methotrexate, vinblastine, adriamycin or epirubicin, and cisplatin (MVA(E)C) and cisplatin with methotrexate (CM) were used [474], and one trial used cisplatin monotherapy [475]. The data were not convincing to support an unequivocal recommendation for the use of adjuvant chemotherapy. In 2014, this meta-analysis was updated with an additional three studies [467-469] resulting in the inclusion of 945 patients from nine trials [466]. None of the trials had fully accrued and individual patient data were not used in the analysis [466]. For one trial only an abstract was available at the time of the meta-analysis [468] and none of the included individual trials 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/cisplatin) [467, 468]. The HR for OS was 0.77 (95% CI: 0.59–0.99, p = 0.049) and for DFS 0.66 (95% CI: 0.45–0.91, p = 0.014) with a stronger impact on DFS in case of nodal positivity. Recently, a systematic review and meta-analysis of individual patient data from RCTs in patients treated with adjuvant cisplatin-based chemotherapy for MIBC was conducted [476]. In an analysis of 10 RCTs (n = 1,183), an OS benefit was demonstrated for cisplatin-based adjuvant chemotherapy (HR: 0.82, 95% CI: 0.70–0.96, p = 0.02). This translates into an absolute improvement in survival of 6% at 5 years, from 50% to 56%, and a 9% absolute benefit when adjusted for age, sex, pT stage, and pN category (HR: 0.77, 95% CI: 0.65–0.92, p = 0.004). Adjuvant chemotherapy was also shown to improve RFS (HR: 0.71, 95% CI: 0.60-0.83, p < 0.001), locoregional RFS (HR: 0.68, 95% CI: 0.55–0.85, p < 0.001), and MFS (HR: 0.79, 95% CI: 0.65–0.95, p = 0.01), with absolute benefits of 11%, 11%, and 8%, respectively.

A retrospective cohort analysis including 3,974 patients after cystectomy and LND showed an OS benefit in high-risk subgroups (extravesical extension and nodal involvement) (HR: 0.75, CI: 0.62–0.90) [477]. A publication of the largest RCT (European Organisation for Research and Treatment of Cancer [EORTC] 30994), although not fully accrued, showed a significant improvement of PFS for immediate, compared with deferred, cisplatin-based chemotherapy (HR: 0.54, 95% CI: 0.4–0.73, p < 0.0001), but there was no significant OS benefit [478]. Furthermore, a large observational study including 5,653 patients with pathological T3–4 and/ or pathological node-positive BC, treated between 2003 and 2006 compared the effectiveness of adjuvant chemotherapy vs. observation. Twenty-three percent of patients received adjuvant chemotherapy with a 5-year OS of 37% for the adjuvant arm vs. 29.1% (HR: 0.70, 95% CI: 0.64–0.76) in the observation group [479]. Another large retrospective analysis based on the U.S. National Cancer Database including 15,397 patients with locally-advanced (pT3/4) or LN-positive disease also demonstrated an OS benefit in patients with UC histology [480]. In patients with concomitant histological subtypes, however, no benefit was found.

Patients should be informed about potential chemotherapy options before RC and the limited evidence for adjuvant chemotherapy.

7.6.2 Role of adjuvant immunotherapy

To determine the benefit of PD-1/PD-L1 checkpoint inhibitors, three phase III RCTs have evaluated checkpoint inhibitor monotherapy with atezolizumab, nivolumab or pembrolizumab in patients with muscle-invasive UC. The CheckMate 274 phase III multi-centre, double-blind, RCT of adjuvant nivolumab vs. placebo for up to 1 year in 709 patients with muscle-invasive UC with a high risk of recurrence (pathological stage pT3, pT4a, or pN+) (neoadjuvant cisplatin-based chemotherapy was allowed before trial entry) demonstrated a significant improvement in median DFS (20.8 months [95% CI: 16.5–27.6] with nivolumab and 10.8 months [95% CI: 8.3–13.9] with placebo). The percentage of patients who were alive and disease-free at 6 months was 74.9% with nivolumab and 60.3% with placebo (HR for disease recurrence or death, 0.70; 98.22% CI: 0.55–0.90; p < 0.001). Among patients with a PD-L1 expression level of ≥ 1% (tumor cell [TC] score), the percentage of patients was 74.5% and 55.7%, respectively (HR: 0.55; 98.72% CI: 0.35–0.85; p < 0.001) [481]. In an analysis using both PD-L1 TC score and combined positive score (CPS), more patients had CPS ≥ 1 than TC ≥ 1% and patients with CPS ≥ 1 had improved DFS with nivolumab which may have contributed to the benefit seen with adjuvant nivolumab in patients with TC < 1% and CPS ≥ 1 [482]. There was no clinically meaningful deterioration in health-related quality of life with adjuvant nivolumab compared to placebo [483].

The primary endpoint of DFS was not achieved in a multi-centre RCT of adjuvant atezolizumab vs. observation in patients with ypT2–4a or ypN+ tumours following NAC or pT3–4a or pN+ tumours if no NAC was received (IMvigor010). Median DFS was 19.4 months (95% CI: 15.9–24.8) with atezolizumab and 16.6 months (11.2–24.8) with observation (stratified HR: 0.89, 95% CI: 0.74–1.08, p = 0.24) [484]. A similarly designed trial of pembrolizumab in the adjuvant setting has completed accrual with results awaited.

The FDA has approved nivolumab for adjuvant treatment of patients with UC who are at high risk of recurrence after undergoing surgery [485] whereas the EMA has approved adjuvant nivolumab for the treatment of adults with muscle-invasive UC (MIUC) with tumour cell PD-L1 expression ≥ 1%, who are at high risk of recurrence after undergoing radical resection of MIUC. A promising report (see Marker section) has suggested a potential role for ctDNA to guide the use of adjuvant IO for UC [486].

7.6.3 Summary of evidence and guidelines for adjuvant therapy

Summary of evidence	LE
Adjuvant cisplatin-based chemotherapy for high-risk patients (pT3, 4 and/or or N+ M0) without neoadjuvant treatment can be associated with improvement in DFS and OS but trials are underpowered to adequately answer this question.	2a
To date, studies of immune checkpoint inhibitors in the adjuvant setting in patients with high-risk MIBC who have or have not received NAC have demonstrated conflicting results with the CheckMate 274 study demonstrating an improvement in DFS with adjuvant nivolumab and the IMvigor 010 study failing to show an improvement in DFS with adjuvant atezolizumab.	1b
Circulating tumour DNA holds promise as both a prognostic and predictive biomarker to guide the use of adjuvant IO for UC in patients who are at a high risk of recurrence and positive for ctDNA treated with adjuvant atezolizumab demonstrating improved outcomes compared with observation.	2b

Recommendations	Strength rating
Offer adjuvant cisplatin-based combination chemotherapy to patients with pT3/4 and/or pN+ disease if no neoadjuvant chemotherapy has been given.	Strong
Offer adjuvant nivolumab to selected patients with pT3/4 and/or pN+ disease not eligible for, or who declined, adjuvant cisplatin-based chemotherapy.	Weak

7.7 Metastatic disease

7.7.1 Introduction

The treatment of metastatic UC had remained largely unchanged since pivotal trials published over 20 years ago set the standard of care for first-line treatment with cisplatin-based combinations demonstrating an OS benefit. This longstanding paradigm was challenged in the past years by the introduction of immunotherapy using checkpoint inhibitors and it was finally upended in October 2023 with the presentation of the results of two practice-changing randomised clinical trials (RCTs) demonstrating an overall survival benefit in the first line setting against platinum-based chemotherapy (EV-302/KEYNOTE A39 and Checkmate 901) [487, 488]. These updated guidelines reflect the results of these two trials and the impact for first and later lines management of patients with metastatic bladder cancer.

7.7.2 *First-line systemic therapy for metastatic disease*

In general, patients with untreated metastatic UC can be divided into two broad categories: eligible for combination therapies or ineligible for combination therapies. The distinction between the two groups is currently based on the eligibility criteria for the pivotal trial EV-302/KEYNOTE 39A and is likely to undergo changes in the near future based on results from real-world evidence investigations. Major criteria include ECOG performance status 0-2, GFR ≥ 30 ml/min and adequate organ functions based on eligibility for treatment with Enfortumab vedotin and Pembrolizumab. With regards to platinum-based chemotherapy the definitions to distinguish patients fit for cisplatin, fit for carboplatin und unfit for any platinum-based therapy remains valid as outlined below and summarised in Table 7.2.

7.7.2.1 Definitions: 'Fit for cisplatin, fit for carboplatin, unfit for any platinum-based chemotherapy'

An international survey among BC experts [432] was the basis for a consensus statement on how to classify patients unfit for cisplatin-based chemotherapy. At least one of the following criteria must be present: PS > 1; GFR ≤ 60 mL/min; grade ≥ 2 audiometric hearing loss; grade ≥ 2 peripheral neuropathy or New York Heart Association (NYHA) class III heart failure [433]. Around 50% of patients with BC are not eligible for cisplatin-based chemotherapy [433]. Renal function assessment is of utmost importance for treatment selection. Measuring GFR with radioisotopes (^{99}mTc DTPA or ^{51}Cr-EDTA) is recommended in equivocal cases.

Cisplatin has also been administered in patients with a lower GFR (40–60 mL/min) using different split-dose schedules. The respective studies were mostly small phase I and II trials in different settings (neoadjuvant and advanced disease) demonstrating that the use of split-dose cisplatin is feasible and appears to result in encouraging efficacy [486, 489, 490]. However, no prospective RCT has compared split-dose cisplatin with conventional dosing.

Most patients that are deemed unfit for cisplatin are able to receive carboplatin-based chemotherapy. However, some patients are deemed unfit for any platinum-based chemotherapy, i.e. both cisplatin and carboplatin. Patient are unfit for any platinum-based chemotherapy in case of PS > 2, GFR < 30 mL/min or the combination of PS 2 and GFR < 60 mL/min since the outcome in this patient population is poor regardless of platinum-based treatment or not [491]. Patients with multiple comorbidities may also be poor candidates for platinum-based chemotherapy.

Table 7.2: Definitions of platinum-eligibility for first-line treatment of metastatic urothelial carcinoma

Platinum-eligible		Platinum-ineligible
Cisplatin-eligible	**Carboplatin-eligible**	
ECOG PS 0-1 *and*	ECOG PS 2 *or* GFR 30–60 mL/min	Any of the following:
GFR > 50–60 mL/min *and*	or not fulfilling other cisplatin-eligibility criteria	GFR < 30 mL/min
Audiometric hearing loss grade < 2 *and*		ECOG PS > 2
Peripheral neuropathy grade < 2 *and*		ECOG PS 2 *and* GFR < 60 mL/min
Cardiac insufficiency NYHA class < III		Comorbidites > Grade 2

ECOG = Eastern Cooperative Oncology Group; GFR = glomerular filtration rate; NYHA = New York Heart Association; PS = performance status.

7.7.2.1 First-line chemotherapy in patients fit for combination therapy

7.7.2.1.1 Enfortumab vedotin plus Pembrolizumab

The combination of Enfortumab vedotin (EV) plus pembrolizumab represents the new standard of care for patients who are deemed fit for combination therapies. This is based on EV-302/KEYNOTE 39A, a phase III trial that tested the antibody drug conjugate EV directed against nectin-4 (EV: administered any number of times until progression) in combination with the immune checkpoint inhibitor, pembrolizumab (maximum of 35 cycles) against platinum-based chemotherapy (cisplatin or carboplatin permitted) in combination with gemcitabine (up to 6 cycles) in the first-line advanced unresectable or metastatic urothelial carcinoma. 30% of the patients in the control arm received switch maintenance immunotherapy with avelumab. Both co-primary endpoints, PFS and OS were clearly met with a significant improvement in median PFS of 12.5 vs 6.3 months (HR 0.45 (0.38-0.54) and median OS of 31.5 vs. 16.1 months (HR 0.47 (0.38-0.58), respectively. The overall ORR was 67.7% including 29.1% complete remissions (CR) compared to 44.4% (12.5% CR) with platinum-based chemotherapy (p<0.00001). All pre-specified subgroups benefited equally from EV+pembrolizumab regardless

of cisplatin eligibility, PD-L1 expression or presence of liver metastases. Treatment-related toxicity grade ≥ 3 was reported in 55% for EV/Pembrolizumab versus 70% in the chemotherapy arm. Specific and relevant EV toxicities include skin rash, peripheral neuropathy, ocular disorders and hyperglycemia. Toxicity of EV/Pembrolizumab needs to be managed proactively and attentively to avoid severe sequelae. The administration of EV/Pembrolizumab requires adequate knowledge and care from a specialised interprofessional team [487].

The combination of EV and pembrolizumab as the first-line treatment in 45 cisplatin-ineligible patients with locally-advanced/metastatic UC was also investigated in EV-103, phase 1b/2 study, and demonstrated a confirmed objective response rate after a median of nine cycles of 73.3% with a complete response rate of 15.6% [492]. The median duration of response and median OS were 25.6 months and 26.1 months, respectively. The most common treatment-related AEs were peripheral sensory neuropathy (55.6%), fatigue (51.1%), and alopecia (48.9%) [492]. A second cohort within the same study randomly assigned previously untreated cisplatin-ineligible patients to EV alone or EV with pembrolizumab [493]. The ORR was 64.5% (95% CI, 52.7 to 75.1) and 45.2% (95% CI, 33.5 to 57.3) for patients treated with EV+ pembrolizumab (N = 76) and EV monotherapy (N = 73), respectively. The median DOR was not reached for the combination and was 13.2 months for monotherapy. Based on these results enfortumab vedotin plus pembrolizumab has been granted FDA accelerated approval for patients with locally advanced or metastatic UC who are ineligible for cisplatin-containing chemotherapy.

7.7.2.1.2 Paitents eligible for combination therapy but not eligible for EV or EV not available

In spite of the very recent results of EV-302/KEYNOTE 39A study, EV will not be available in different countries. Moreover, some patients might not be eligible for or refuse treatment with EV including patients with uncontrolled diabetes, peripheral neuropathy grade ≥ 2 and pre-existing significant skin disorders. Platinum-based chemotherapy with integration of checkpoint inhibitors represents the preferred options in such patients. The general presumptions for cisplatin- and carboplatin-based therapy remain unchanged in this case and are outlined below.

7.7.2.1.2.1 Patients fit for cisplatin

Cisplatin-containing combination chemotherapy was the standard of care since the late 1980s demonstrating an OS of 12 to 14 months in different series (for a review see [494]). Methotrexate, vinblastine, adriamycin plus cisplatin and GC achieved survival of 14.8 and 13.8 months, respectively [495]. Overall response rates were 46% for MVAC and 49% for GC. The lower toxicity of GC [200] compared to standard MVAC has resulted in GC becoming the standard regimen.

Dose-dense MVAC combined with granulocyte colony-stimulating factor (G-CSF) is less toxic and more efficacious than standard MVAC in terms of, complete response (CR), and 2-year OS. However, there is no significant difference in median survival between the two regimens [496, 497]. Further intensification of treatment using paclitaxel, cisplatin and gemcitabine (PCG) triplet regimen did not result in a significant improvement in OS in the intention-to-treat (ITT) population of a phase III RCT, comparing PCG to GC [498]. Similarly, the addition of the angiogenesis inhibitor bevacizumab to GC did not result in OS improvement [499].

The disease sites have an impact on long-term survival. In LN-only disease, 20.9% of patients were alive at five years compared to only 6.8% of patients with visceral metastases [495]. In the trials with long-term follow-up, approximately 10-15% of patients with metastatic UC were alive at 5 years and longer, suggesting a sustained benefit from cisplatin-based chemotherapy in a minority of patients [495, 497].

Carboplatin-containing chemotherapy, without the inclusion of immunotherapy, is not considered to be equivalent to cisplatin-based combinations, and should not be considered interchangeable or standard in patients fit for cisplatin. A comparative analysis of four randomised phase II trials of carboplatin vs. cisplatin combination chemotherapy demonstrated lower CR rates and shorter OS for the carboplatin arms [500]. A retrospective study highlighted the importance of applying cisplatin in cisplatin-eligible patients in order to maintain benefit [501].

Switch maintenance with immunotherapy after platinum-based chemotherapy

A randomised phase II trial evaluated switch maintenance treatment with pembrolizumab in patients achieving at least stable disease on platinum-based first-line chemotherapy. The primary endpoint of PFS was met (5.4 months vs. 3.0 months, HR: 0.65, p = 0.04) [502].

The JAVELIN Bladder 100 study investigated the impact of switch maintenance with the PD-L1 inhibitor avelumab after initial treatment with platinum-gemcitabine chemotherapy. Patients achieving at least stable disease or better after 4–6 cycles of platinum-gemcitabine were randomised to avelumab or best supportive care (BSC). Overall survival was the primary endpoint which improved to 21.4 months with avelumab compared to 14.3 months with BSC (HR: 0.69, 95% CI: 0.56–0.86; p < 0.001). Of patients who discontinued BSC and received subsequent treatment 53% received immunotherapy. Immune-related AEs occurred in 29% of all patients and 7% experienced grade 3 complications [503]. Patient-reported ouctomes from JAVELIN Bladder 100 demonstrated no detrimental effect on quality of life [504].

Maintenance IO with avelumab was until recently standard of care for all patients with at least stable disease on first-line platinum-based chemotherapy.

If patients are fit for cisplatin, the results of CheckMate 901 should be considered [488]. This trial tested the addition of nivolumab in combination with gemcitabine/cisplatin (GC) and followed by nivolumab maintenance (until progression or maximum of 24 months) compared to GC alone. Of note, only 9% in the control arm received switch maintenance therapy with avelumab. The co-primary endpoints, PFS and OS were reached with a median PFS of 7.9 vs 7.6 months (HR 0.72, 95%CI 0.59-0.88) and a median OS of 21.7 vs. 18.9 months (HR 0.78, 95%CI 0.63-0.96). The response rate was improved with GC plus Nivolumab (57.6% vs 43.1.%). A complete remission (CR) was achieved in 21.7% of patients with Nivolumab plus GC with a duration of 37.1 months. Nivolumab plus GC had higher treatment related grade ≥3 toxicity (62% vs 52%). This combination represents an alternative to GC followed by maintenance therapy with avelumab in patients not eligible for EV or if EV is not available.

7.7.2.1.2.2 Patients fit for carboplatin (but unfit for cisplatin)

Up to 50% of patients are not fit for cisplatin-containing chemotherapy but most may be candidates for carboplatin [433]. A randomised phase II/III trial in this setting was conducted by the EORTC and compared two carboplatin-containing regimens (methotrexate/carboplatin/vinblastine [M-CAVI] and gemcitabine/carboplatin [GemCarbo]) in patients unfit for cisplatin. The EORTC definitions for eligibility were GFR < 60 mL/min and/or PS 2. Severe acute toxicity was 13.6% with GemCarbo vs. 23% with M-CAVI, while the ORR was 42% for GemCarbo and 30% for M-CAVI, respectively [491]. Based on these results the combination of carboplatin and gemcitabine should be considered a standard of care in this patient group. Importantly, both EV-302/KEYNOTE 39A and JAVELIN Bladder 100 included patients fit for carboplatin, while CheckMate 901 included patients fit for cisplatin only.

Combinations of gemcitabine and paclitaxel have been studied as first-line treatment and produced response rates between 38% and 60% but has never been tested in RCTs [505-507]. A randomised phase II trial assessed the efficacy and tolerability profile of two vinflunine-based regimens (vinflunine/gemcitabine vs. vinflunine/carboplatin). Both regimens showed equal ORR and OS with less haematologic toxicity for the combination of vinflunine/gemcitabine [508]. Non-platinum combination chemotherapy is nevertheless not recommended for first-line use in platinum-eligible patients.

The use of single-agent chemotherapy has been associated with varying response rates. Responses with single agents are usually short, complete responses are rare, and no long-term DFS/OS has been reported. It is not recommended for first-line treatment of metastatic UC.

7.7.2.2 First line therapy in patients not eligible for combination therapy

Limited data exist regarding the optimal treatment for this patient population which is characterised by severely impaired PS (PS > 2) and/or severely impaired renal function (GFR < 30 mL/min) or inadequate organ function. Historically, the outcome in this patient group has been poor. Best supportive care has often been chosen instead of systemic therapy. Most trials evaluating alternative treatment options to cisplatinum-based chemotherapy did not focus specifically on this patient population, making data interpretation difficult. The FDA (but not EMA) has approved pembrolizumab as a first-line treatment for patients not fit to receive any platinum-based chemotherapy regardless of PD-L1 status based on the results of one single-arm phase II trial [509].

Based on the results of two single arm phase II trials trials [509, 510] the checkpoint inhibitors pembrolizumab and atezolizumab have been approved by EMA for first-line treatment in cisplatin- unfit patients in case of positive PD-L1 status. PD-L1 positivity for use of pembrolizumab is defined by immunohistochemistry as a CPS of ≥ 10 using the Dako 22C33 platform and for atezolizumab as positivity of ≥ 5% tumour-infiltrating immune cells using Ventana SP142.

Pembrolizumab was tested in 370 patients with advanced or metastatic UC ineligible for cisplatin, showing an ORR of 29% and CR in 7% of patients [509, 511]. Atezolizumab was evaluated in the same patient population in a phase II trial (n = 119) showing an ORR of 23% with 9% of patients achieving CR [510].

First-line avelumab was evaluated in patients with PD-L1 positive, metastatic or locally advanced disease and demonstrated a median OS of 10.0 months (95% CI: 5.5-14.5 months) with 43% of patients alive at 1 year. A complete response was achieved in 8.5% of patients, and 15.5% had a partial response [512].

A phase 2 randomised trial (BAYOU) evaluating durvalumab with olaparib or placebo in platinum-ineligible patients with metastatic UC demonstrated no PFS or OS benefit for the addition of olaparib; however, in a secondary analysis of patients with homologous recombination repair gene mutations, PFS was improved with the addition of olaparib as compared to placebo (median PFS was 5.6 months (95% CI, 1.9 to 8.1) versus 1.8 months (95% CI, 1.7 to 2.2), (HR, 0.18; 95% CI, 0.06 to 0.47) [513].

The trials IMvigor 130, Keynote 361 and DANUBE all included an experimental arm with immunotherapy alone using atezolizumab, pembrolizumab and durvalumab, respectively [514-516]. No benefit in terms of PFS or OS for the use of single-agent immunotherapy compared to platinum-based chemotherapy was found. The combination of carboplatin/gemcitabine therefore is still considered the preferred first-line treatment choice for patients planned to receive chemotherapy who are ineligible for cisplatin.

7.7.2.3 Results of other trials integrating immunotherapy in the first line setting without OS benefit

In 2020, the results of three phase III trials were published investigating the use of immunotherapy in the first-line setting for platinum-eligible patients. The first trial to report was IMvigor130 investigating the combination of the PD-L1 inhibitor atezolizumab plus platinum-gemcitabine chemotherapy vs. chemotherapy plus placebo vs. atezolizumab alone [514]. The primary endpoint of PFS benefit for the combination vs. chemotherapy alone in the ITT group was reached (8.2 months vs. 6.3 months [HR: 0.82, 95% CI: 0.70–0.96; one-sided, p = 0.007]) while OS was not significant at the interim analysis after a median follow-up of 11.8 months. The small PFS benefit in the absence of an OS benefit has raised questions of its clinical significance.

The KEYNOTE 361 study had a very similar design using the PD-1 inhibitor pembrolizumab plus platinum-gemcitabine vs. chemotherapy plus placebo vs. pembrolizumab alone. The results of the primary endpoints of PFS and OS for the comparison of pembrolizumab plus chemotherapy vs. chemotherapy plus placebo in the ITT population showed no benefit for the combination [515].

DANUBE compared the immunotherapy combination (IO-IO) of CTLA-4 inhibitor tremelimumab and PD-L1 inhibitor durvalumab with chemotherapy alone or durvalumab alone [516]. The co-primary endpoint of improved OS for the IO-IO combination vs. chemotherapy was not reached in the ITT group nor was the OS improved for durvalumab monotherapy vs. chemotherapy in the PD-L1-positive population.

In conclusion, unlike CheckMate 901, these three trials do not support the use of combination of the PD-1/L1 checkpoint inhibitors plus platinum-based chemotherapy or the IO-IO combination as first-line treatment.

*7.7.3 **Further-line systemic therapy for metastatic disease***

7.7.3.1 Introduction

Due to the results of the EV-302/KEYNOTE A39 trial and the expected paradigm shift in first-line therapy with establishment of the EV plus Pembrolizumab combination, as well as the CheckMate 901 trial with the combination of cisplatin, gemcitabine and nivolumab, selecting subsequent therapy lines in patients who fail during or progress after first-line treatment poses a significant challenge. Depending on the choice of first-line therapy the following options exist.

7.7.3.2 Chemotherapy

In patients eligible for combination therapy having received EV plus pembrolizumab, platinum-based chemotherapy with gemcitabine plus cisplatin or carboplatin may be considered, however, data is limited for this new post EV plus pembrolizumab clinical disease state and toxicities, e.g. neuropathy from prior therapy must be taken into consideration in determining a treatment plan. For patients already having received platinum-based chemotherapy with or without immunotherapy further -line chemotherapy data are highly variable and mainly derive from small single-arm phase II trials apart from one single phase III RCT. A reasonable strategy has been to re-challenge former platinum-sensitive patients if progression occurred at least six to twelve months after first-line platinum-based combination chemotherapy. A retrospective analysis of 296 patients within the RISC cohort (Retrospective International Study of Cancers of the Urothelium) revealed that subsequent platinum-based combination chemotherapy achieved a somewhat higher disease control rate (57.4% vs. 44.8%, p.= 0.041) and OS (7.9 vs. 5.5 months, p = 0.035) compared to subsequent non-platinum-based chemotherapy [517]. Second-line response rates of single-agent treatment with paclitaxel (weekly), docetaxel, gemcitabine, nab-paclitaxel, oxaliplatin, ifosfamide, topotecan, pemetrexed, lapatinib, gefitinib and bortezomib have ranged between 0% and 28% in small phase II trials [518, 519].

The paclitaxel/gemcitabine combination has shown good response rates in small single-arm studies but no adequate phase III RCT has been conducted [520, 521]. Vinflunine was tested in a phase III RCT and compared against BSC in patients progressing after first-line treatment with platinum-based chemotherapy [522]. The results showed a very modest ORR (8.6%), a clinical benefit with a favourable safety profile and a survival benefit, which was however only statistically significant in the eligible patient population (not in the ITT population). A randomised phase III trial evaluated the addition of the angiogenesis inhibitor ramucirumab to docetaxel chemotherapy vs. docetaxel alone, which resulted in improved PFS (4.1 vs. 2.8 months) and higher response rates (24.5% vs. 14%) but no OS benefit was achieved [523, 524].

7.7.3.3 Immunotherapy for platinum-pre-treated patients without previous immunotherapy

The immune checkpoint inhibitors pembrolizumab, nivolumab, atezolizumab, avelumab, and durvalumab have demonstrated similar efficacy and safety in patients progressing during, or after, previous platinum-based chemotherapy in phase I, II and III trials.

Pembrolizumab demonstrated a significant OS Improvement as second-line treatment in a phase III RCT leading to EMA and FDA approval. Patients (n = 542) were randomised to receive either pembrolizumab monotherapy or chemotherapy (paclitaxel, docetaxel or vinflunine). The median OS with pembrolizumab was 10.3 months (95% CI: 8.0–11.8) vs. 7.4 months (95% CI: 6.1–8.3) with chemotherapy (HR 0.73, 95% CI: 0.59–0.91, p = 0.002) independent of PD-L1 expression levels [511, 525].

Atezolizumab was the first checkpoint inhibitor approved by the FDA for metastatic UC based on the results of phase I and II trials [236, 526], however, the indication has subsequently been withdrawn. The phase III RCT (IMvigor211) included 931 patients comparing atezolizumab with second-line chemotherapy (paclitaxel, docetaxel or vinflunine) did not meet its primary endpoint of improved OS for patients with high PD-L1 expression with 11.1 months (atezolizumab) vs. 10.6 (chemotherapy) months (stratified HR: 0.87, 95% CI: 0.63–1.21, p = 0.41) [470].

The PD-1 inhibitor nivolumab was approved by the FDA based on the results of a single-arm phase II trial (CheckMate 275), enrolling 270 platinum pre-treated patients. The primary endpoint of ORR was 19.6%, and OS was 8.74 months for the entire group [527]. The TITAN-TCC study evaluated the safety and activity of nivolumab induction plus high-dose ipilumumab (3 mg/kg) boosts in non-responders (stable or progressive disease) in the second-line treatment of 83 patients with metatsatic UC. Fifty (60%) received at least one boost with an investigator-assessed response rate of 33% (CR: 7%), demonstrating promising outcomes with this strategy compared to the rate reported in CheckMate 275 [528].

7.7.3.4 Side-effect profile of immunotherapy

Checkpoint inhibitors including PD-1 or PD-L1 antibodies and CTLA-4 antibodies have a distinct side-effect profile associated with their mechanism of action leading to enhanced immune system activity. These AEs can affect any organ in the body leading to mild, moderate or severe side effects. The most common organs affected are the skin, GI tract, liver, lung, thyroid, adrenal and pituitary gland. Other systems that may be affected include musculoskeletal, renal, nervous, haematologic, ocular and cardiovascular system. Any change during immunotherapy treatment should raise suspicion about a possible relation to the treatment. The nature of immune-related AEs has been very well characterised and published [529]. The timely and appropriate treatment of immune-related side effects is crucial to achieve optimal benefit from the treatment while maintaining safety. Clear guidelines for side-effect management have been published [530]. Immunotherapy treatment should be applied and supervised by trained clinicians only to ensure early side effect recognition and treatment. In case of interruption of immunotherapy, re-challenge will require close monitoring for AEs [531].

7.7.4 ***Integration of other agents***

7.7.4.1 Antibody drug conjugates Enfortumab vedotin monotherapy

The first antibody drug conjugate to report encouraging data in patients previously treated with platinum-based chemotherapy and checkpoint inhibition was EV. The phase-II single-arm study EV-201 in 125 patients showed a confirmed objective response rate of 44%, including 12% complete responses [532]. This data led to accelerated FDA and EMA approval for EV in locally-advanced or metastatic UC patients who previously received a PD-1 or PD-L1 inhibitor and platinum-containing chemotherapy, as well as for cisplatin-ineligible patients who received one or more prior lines of therapy [533, 534]. Another cohort of the same EV-201 trial demonstrated similar promising results in 91 patients that were cisplatin-ineligible and had received prior IO [535]. A phase III RCT (n = 608) comparing EV with single-agent chemotherapy after prior platinum chemotherapy and checkpoint inhibitor immunotherapy demonstrated significant survival benefit of almost 4 months (12.88 months vs. 8.97 months; HR 0.7, 95% CI: 0.56–0.89) [536]. The most common treatment-related AEs included alopecia (45%), peripheral

neuropathy (34%), fatigue (31%, 7.4% ≥ grade 3), decreased appetite (31%), diarrhoea (24%), nausea (23%) and skin rash (16%, 7.4% ≥ grade 3).

7.7.4.2 Antibody drug conjugate Sacituzumab govetican

Another new and also promising antibody drug conjugate is sacituzumab govitecan, consisting of a humanised monoclonal antibody targeting trophoblast cell surface antigen 2 (Trop-2) conjugated to SN-38, the active metabolite of irinotecan. Sacituzumab govitecan was tested in 113 platinum and immunotherapy pre-treated metastatic UC (mUC) patients [532] and achieved an ORR of 27% and a total of 77% had a decrease in measurable disease, median PFS was 5.4 months and median OS 10.9 months [537]. Side effects consisted of haematological toxicities (neutropenia 34% ≥ grade 3; febrile neutropenia 10% ≥ grade 3), fatigue (52%), alopecia (47%), nausea (60%), diarrhea (65%, 10% ≥ grade 3) and decreased appetite (36%) [537]. Sacituzumab govitecan has received accelerated FDA approval for metastatic UC with prior platinum and IO pre-treatment. Several trials using sacituzumab govitecan as monotherapy or in combination are ongoing.

7.7.4.3 FGFR inhibition

Genomic profiling of UC has revealed common potentially actionable genomic alterations including alterations in FGFR [538]. Erdafitinib is a pan-FGFR tyrosine kinase inhibitor and the first FDA-approved targeted therapy for mUC with susceptible FGFR2/3 alterations following platinum-containing chemotherapy. The phase II trial of erdafitinib included 99 patients whose tumour harboured an FGFR3 mutation or FGFR2/3 fusion and who had disease progression following chemotherapy [234]. The confirmed ORR was 40% and an additional 39% of patients had stable disease. A total of 22 patients had previously received immunotherapy with only one patient achieving a response, yet the response rate for erdafitinib for this subgroup was 59%. At a median follow-up of 24 months, the median PFS was 5.5 months (95% CI: 4.0–6.0) and the median OS was 11.3 months (95% CI: 9.7–15.2) [234]. Treatment-related AEs of ≥ grade 3 occurred in 46% of patients. Common AEs of ≥ grade 3 were hyponatraemia (11%), stomatitis (10%), and asthenia (7%) and 13 patients discontinued erdafitinib due to AEs, including retinal pigment epithelial detachment, hand-foot syndrome, dry mouth, and skin/nail events. In a long-term follow up, the efficacy and safety profile remained similar with no new safety signals with longer follow-up [539].

In the recent THOR cohort 1 trial, a phase 3 trial of erdafitinib as compared with chemotherapy (docetaxel or vinflunine) in patients with metastatic UC with susceptible FGFR3/2 alterations who had progression after one or two previous treatments that included an anti–PD-1 or anti–PD-L1 demonstrated an improvement in OS with erdafitinib as compared to chemotherapy (12.1 months vs. 7.8 months; HR 0.64 (0.47 to 0.88); P=0.005). Median PFS was also longer with erdafitinib than with chemotherapy (5.6 vs. 2.7 months; (HR 0.58 (0.44 -0.78) [540]. Treatment-related toxicity grade ≥ 3 was similar in the two groups. The most common treatment-related adverse events of grade 3 or higher were palmar–plantar erythrodysesthesia syndrome (9.6%), stomatitis (8.1%), onycholysis (5.9%), and hyperphosphatemia (5.2%) in the erdafitinib group.

Data on cohort 2 with 351 patients, anti-PD-(l1) naïve and progressing after one prior treatment line compared Erdafitinib with pembrolizumab. No difference in the primary endpoint OS was detected (10.9 versus 11.1 months, HR 1.18 (0.92-1.51) [541]. Overall response rate was 40.0% and 21.6% and median duration of response was 4.3 and 14.4 months for erdafitinib and pembrolizumab, respectively. 64.7% and 50.9% of patients in the erdafitinib and pembrolizumab arms had ≥ 1 grade 3-4 adverse events.

In addition to erdafitinib, several other FGFR inhibitors are being evaluated including infigratinib which has demonstrated promising activity [235]. A phase 2/3 trial of the pan-FGFR inhibitor, rogaratinib versus chemotherapy in patients with locally advanced or metastatic UC with FGFR1-3 mRNA overexpression demonstrated similar outcomes as compared to chemotherapy [542]. The increased identification of FGFR3 mutations/fusion has led to several ongoing trials with different agents and combinations in different disease settings.

*7.7.5 **Current status of predictive biomarkers***

The most important advance in recent years has been the recognition of alterations in FGFR3 including mutations and gene fusions as a predictive marker for response to FGFR inhibitors [234]. It is recommended to screen mUC patients ideally at diagnosis of metastatic disease for FGFR3 alterations to plan optimal treatment including trials.

Many efforts have focused on markers for predicting response to immune checkpoint inhibition. Programmed death-ligand 1 expression by immunohistochemistry has been evaluated in many studies with mixed and, so far, inconclusive results. This may in part be related to the use of different antibodies and various scoring systems evaluating different compartments i.e., tumour cells, immune cells, or both. A major limitation of PD-L1 staining relates to the significant proportion of PD-L1-negative patients that respond to immune

checkpoint blockade. The predictive value of PD-L1 was not confirmed in large phase III trials evaluating the integration of immunotherapy in the first-line setting for mUC [514-516]. At present, the only indication for PD-L1 testing in mUC is dictated by current EMA approvals and relates to the potential use of immune checkpoint inhibitors as first-line monotherapy in patients unfit for cisplatin-containing chemotherapy.

Another biomarker that has been evaluated for predicting response to immunotherapy is high TMB [238]. Neoantigen burden and TMB have been associated with response to immune checkpoint blockade in several malignancies. High TMB has been associated with response to immune checkpoint inhibitors in metastatic UC in small single-arm trials [236, 239] but was not confirmed so far in RCTs. Other markers that have been evaluated in predicting response to immune checkpoint inhibitors include molecular subtypes, CD8 expression by immunohistochemistry and other immune gene cell signatures. Recent work has focused on the importance of stroma including the role of TGFs in predicting response to immune checkpoint blockade [242, 243].

In conclusion, apart from FGFR3 alterations, there are currently no further validated predictive molecular markers that are routinely used in clinical practice.

*7.7.6 **Special situations***

7.7.6.1 Impact of prior neoadjuvant/adjuvant therapy on treatment sequence

Peri-operative systemic treatment is increasingly used in UC including cisplatin-based chemotherapy in the neoadjuvant setting for BC and adjuvant platinum-based chemotherapy for upper tract UC [543]. Many ongoing phase III trials investigate the use of immunotherapy in this setting as well (see Section 7.6.2). So far, one trial has reported a significant DFS benefit for adjuvant treatment with nivolumab compared with placebo whereas one trial reported no significant benefit using atezolizumab vs. placebo in the same setting whilst another trial reported negative findings [481, 484]. It is expected that an increased number of patients with metastatic UC will have received pre-treatment with platinum and/or immunotherapy agents. No prospective trials have investigated the treatment of such patients. The choice of treatment in these patients depends on the applied peri-operative treatment and the time until relapse. If at least 12 months have passed since the end of peri-operative treatment the same systemic treatment as in treatment-naive patients is recommended.

7.7.6.2 Systemic treatment of metastatic disease with histology other than pure urothelial carcinoma

Pure UC represents the predominant histology in over 90% of patients with mUC. subtypes (e.g. micropapillary, nested, sarcomatoid) and divergent differentiation (e.g., SCC, adenocarcinoma) can be found in addition to pure UC in up to 33% of patients. Such patients were often excluded from large phase II and phase III trials and therefore the knowledge about the best management of such patients is limited. The respective literature was reviewed recently [66] and an expert Delphi survey and consensus conference provided guidance [82]. In case of predominant pure UC it is recommended to treat patients with mixed histology the same way as patients with a pure UC histology. Patients with predominant non-urothelial differentiation such as small cell neuroendocrine carcinoma, urachal adenocarcinoma, SCC and adenocarcinoma should be treated individually.

*7.7.7 **Treatment of patients with bone metastases***

The prevalence of metastatic bone disease (MBD) in patients with advanced/metastatic UC is 30–40% [544]. Interestingly, a recent report described several observations related to age- and sex-related differences in the distribution of metastases in patients with metastatic BC and demonstrated that bone was the most common metastatic site in men with other differences noted according to patient age and sex [545]. Skeletal complications due to MBD have a detrimental effect on pain and QoL and are also associated with increased mortality [546]. Bisphosphonates such as zoledronic acid reduce and delay skeletal-related events (SREs) due to bone metastases by inhibiting bone resorption, as shown in a small pilot study [547]. Denosumab, a fully human monoclonal antibody that binds to and neutralises RANKL (receptor activator of nuclear factor κB ligand), was shown to be non-inferior to zoledronic acid in preventing or delaying SREs in patients with solid tumours and advanced MBD, including patients with UC [548]. Patients with MBD, irrespective of the cancer type, should be considered for bone-targeted treatment [546].

Patients treated with zoledronic acid or denosumab should be informed about possible side effects including osteonecrosis of the jaw and hypocalcaemia. Supplementation with calcium and vitamin D is mandatory. Dosing regimens of zoledronic acid should follow regulatory recommendations and have to be adjusted according to pre-existing medical conditions, especially renal function [549]. For denosumab, no dose adjustments are required for variations in renal function.

7.7.8 Summary: treatment algorithm for metastatic urothelial cancer update 2024

Figure 7.2 summarises the treatment algorithm for metastatic BC based on the evidence discussed in the text above. Patients with treatment-naive mUC can be divided into two broad categories: eligible for combination therapies or ineligible for combination therapies. The distinction between the two groups is currently based on the eligibility criteria for the pivotal trial EV-302/KEYNOTE 39A. Criteria include ECOG performance status 0-2, GFR ≥30ml/min and adequate organ functions with eligibility for treatment with EV and Pembrolizumab.

The combination of EV plus the checkpoint inhibitor pembrolizumab represents the new standard of care for patients who are deemed fit for combination therapies. In patients that might not be eligible for or refuse treatment with EV including patients with uncontrolled diabetes, peripheral neuropathy grade ≥2 and pre-existing significant skin disorders, platinum-based chemotherapy with integration of immune checkpoint inhibitors represents the preferred options.

With regards to platinum-based chemotherapy, the definitions are grouped according to platinum-eligibility based on clear definitions. In platinum-based chemotherapy, cisplatin is to be preferred to carboplatin. Patients who are cisplatin-ineligible but carboplatin-eligible should receive gemcitabine- carboplatin combination chemotherapy. In case of positive PD-L1 status, treatment with checkpoint inhibitors (atezolizumab or pembrolizumab) could be an alternative option.

Patients unfit for both cisplatin and carboplatin (platinum-unfit) can be considered for immunotherapy (FDA approved irrespective of PD-L1 status, EMA approved only for PD-L1 positive patients) or receive BSC.

In cases of disease stabilization or better on platinum-based chemotherapy switch, maintenance treatment with IO (avelumab) is recommended. Alternatively, patients can be followed closely and receive second-line immunotherapy at the time of progression (pembrolizumab).

It is recommended to determine FGFR mutation status before deciding about further-line treatment. Patients with FGFR3 mutations are candidates for FGFR inhibitor treatment.

Enfortumab vedotin therapy is standard in case of progression after platinum chemotherapy and IO, however based on EV-302/KEYNOTE 39A, the majority of patients will be candidates for EV plus pembrolizumab in the first-line setting. The optimal sequence of novel agents and potential combinations are the subject of many ongoing trials. It is generally recommended to treat patients within ongoing clinical trials whenever possible.

7.7.9 Summary of evidence and recommendations for metastatic disease

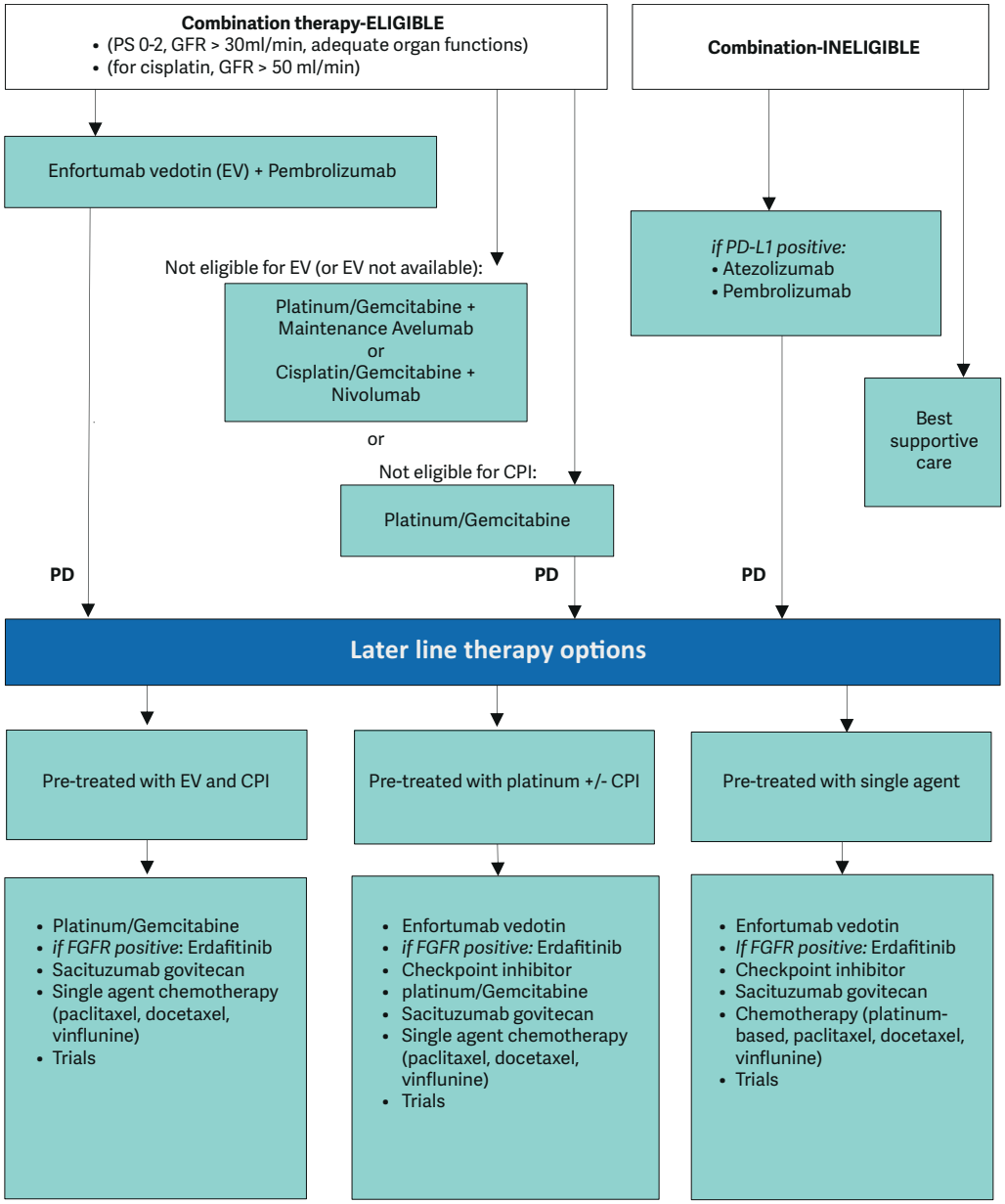
Summary of evidence	LE
Enfortumab vedotin in combination with pembrolizumab in the first-line setting demonstrated significant survival benefit as compared to chemotherapy.	1
The combination of cisplatin and gemcitabine plus Nivolumab in the first-line setting demonstrated significant survival benefit as compared to chemotherapy alone.	1b
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 DFS 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
There is no defined standard therapy for platinum chemotherapy-unfit patients with advanced or metastatic UC.	2b
Post-chemotherapy surgery after partial or complete response may contribute to long-term DFS in highly selected patients.	3
Zoledronic acid and denosumab have been approved for supportive treatment in case of bone metastases of all cancer types including UC, as they reduce and delay skeletal related events.	1b

PD-1 inhibitor pembrolizumab has been approved for patients that have progressed during or after previous platinum-based chemotherapy based on the results of a phase III trial.	1b
Enfortumab vedotin after prior platinum chemotherapy and checkpoint inhibitor immunotherapy has demonstrated a significant survival benefit as compared to chemotherapy.	1b
PD-1 inhibitor atezolizumab is approved for patients with advanced or metastatic UC unfit for cisplatin-based chemotherapy in case of high PD-L1 expression defined as tumour-infiltrating immune cells covering ≥ 5% of the tumour area using the SP142 assay.	1b
PD-1 inhibitor pembrolizumab is approved for patients with advanced or metastatic UC unfit for any platinum-based chemotherapy in case of high PD-L1 expression defined as CPS of ≥ 10 using the Dako 22C33 platform (EMA; FDA approval independent of PD-L1 status).	1b
The combination of chemotherapy plus pembrolizumab or atezolizumab and the combination of durvalumab and tremelimumab have not demonstrated OS survival benefit compared to platinum-based chemotherapy alone.	1b
Switch maintenance with the PD-L1 inhibitor avelumab has demonstrated significant OS benefit in patients achieving at least stable disease on first-line platinum-based chemotherapy.	1b

Recommendations	**Strength rating**
First-line treatment if eligible for combination therapy	
Use antibody drug conjugate enfortumab vedotin (EV) in combination with checkpoint inhibitor (CPI) pembrolizumab.	Strong
If contraindications for EV or EV not available: Offer platinum-containing combination chemotherapy (cisplatin or carboplatin plus gemcitabine) followed by maintenance treatment with CPI avelumab in patients with at least stable disease on chemotherapy.	Strong
If contraindications for EV (or EV not available) and cisplatin-eligible: Consider cisplatin/gemcitabine in combination with CPI nivolumab.	Strong
If contraindications for checkpoint inhibitor therapy: Use platinum-containing combination chemotherapy (Cisplatin or carboplatin plus gemcitabine).	Strong
First-line treatment if not eligible for combination therapy	
Consider single agent CPI pembrolizumab or atezolizumab in case of high PD-1 expression. (for definitions see text).	Weak
Second-line treatment	
After prior EV + CPI	
Offer platinum-containing combination chemotherapy (cisplatin or carboplatin plus gemcitabine).	Weak
If actionable FGFR alterations: offer erdafitinib.	Weak
Consider antibody drug conjugate sacituzumab govitecan.	Weak
Consider single agent chemotherapy (docetaxel, paclitaxel, vinflunine).	Weak
After prior platinum-based chemotherapy +/- CPI	
Offer antibody drug conjugate enfortumab vedotin.	Strong
If actionable FGFR alterations: offer erdafitinib.	Strong
If no prior CPI: offer pembrolizumab.	Strong
Consider antibody drug conjugate sacituzumab govitecan.	Weak
Consider single agent chemotherapy (docetaxel, paclitaxel, vinflunine).	Weak
Further treatment after EV, CPI, platinum-based therapy	
General statement: Offer treatment in clinical trials. Consider best supportive care (BSC) alone if patient is not a candidate for further cancer-specific systemic therapy.	Strong
If actionable FGFR alterations: offer Erdafitinib.	Weak

BSC = best supportive care; CPI = checkpoint inhibitor; EV = enfortumab vedotin; GC = gemcitabine plus cisplatin; FGFR = fibroblast growth factor receptor

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



**EV = enfortumab vedotin; FGFR = fibroblast growth factor receptor; GFR = glomerular filtration rate; PS = performance status; CPI=checkpoint inhibitor; PD-L1= programmed deathligand 1; PD= programmed death*

7.8 Quality of life

7.8.1 Introduction

The evaluation of HRQoL considers physical, psychological, emotional and social functioning. In patients with MIBC, HRQoL is affected, particularly in the physical and social functioning domains [550, 551].

Several questionnaires have been validated for assessing HRQoL in patients with BC, including FACT-G [552], EORTC QLQ-C30/BLM30 [553], SF-36 [554] and the Bladder Cancer Index (BCI) [555]. In spite of these validated questionnaires, there is heterogeneity in the measurements used to assess sexual health. A health questionnaire that covers the entire range of sexual health in bladder cancer patients is currently lacking [556].

Regardless of the which questionnaire is used, assessment of the baseline and post-treatment HRQoL is important. Questionnaires are helpful tools in clinical decision making, but, in addition, data support the prognostic value of baseline HRQoL [557]. In a large population-based study of patients with MIBC and no prior psychiatric history, 31% of all patients with MIBC were diagnosed with a new mental health disorder after their bladder cancer diagnosis [558].

7.8.2 ***Neoadjuvant chemotherapy***

Two RCTs including patiens undergoing NAC have published their HRQoL data [459, 559]. Huddart *et al.*, analysed the subset of patients within the BC2001 trial who underwent NAC prior to (chemo)radiation. Using the FACT-BL questionnaire, no detrimental impact of NAC on HRQoL was observed [459]. Kitamura *et al.*, reported on 64 patients included in the JCOG0209 study who underwent NAC (MVAC vs. MVAC and RC). An overall decline on HRQoL was reported directly following NAC using the FACT-BL questionnaire. However, no difference in HRQoL was observed after the consolidating RC.

7.8.3 ***Radical cystectomy and urinary diversion***

Two systematic reviews and meta-analyses focused on HRQoL after RC and urinary diversion [366, 560].

Yang *et al.*, compared HRQoL of incontinent and continent urinary diversions (all types) including 29 studies (n = 3,754) of which 9 had a prospective design (one of which was randomised) [366]. Only three studies reported HRQoL data both pre- and post-operatively. All these three studies reported an initial deterioration in overall HRQoL but general health, functional and emotional domains at 12 months post-surgery were equal or better than baseline. Overall, no difference in HRQoL between continent and incontinent urinary diversion was reported although an ileal conduit may confer a small physical health benefit [560].

Cerruto *et al.*, reported HRQoL comparing ileal conduit with orthotopic neobladder reconstruction [560]. A pooled analysis was performed including 18 studies (n = 1,553) of which the vast majority were retrospective studies. Although this study was hampered by methodological limitations, no statistical significant difference in overall HRQoL was found.

Altogether, there appears to be no superior type of urinary diversion in terms of overall HRQoL but it is rather a result of proper patient selection. An older and isolated patient is probably better served with an ileal conduit, whereas a younger patient with a higher level of interest in body image and sexuality is better off with an orthotopic diversion. The patient's choice is the key to the selection of reconstruction method [366].

A number of RCTs comparing ORC with RARC (with either intra- or extracorporeal urinary diversion) have reported their HRQoL data [358, 561-563]. All studies reported no statistical significant difference in HRQoL outcomes between surgical techniques.

7.8.4 ***Adjuvant therapy***

HRQoL data was reported in the phase 3 Checkmate 274 RCT where patients were randomised for adjuvant nivolumab or placebo after radical surgery for bladder cancer or UTUC. Patients were not pre-treated with NAC. No clinically meaningful detoration in HRQoL was observed during nivolumab treatment (based on the EORTC QLQ-C30/VAS questionnaire) [483].

7.8.5 ***Bladder-sparing trimodality therapy***

The only HRQoL data in bladder sparing treatment collected in a RCT setting was published by Huddart *et al.* [459]. The primary endpoint was the change in the Bladder Cancer Subscale (BLCS), as part of the FACT-BL questionnaire, at one year post-treatment. Questionnaire return rate at one and five years was 70% and 60%, respectively. A reduction in HRQoL was seen in the majority of the domains immediately following RT, however, in most patients the HRQoL scores returned to baseline 6 months after RT and maintained at this level for five years. Approximately 33% of patients reported persistent lower Bladder Cancer Subscale scores after five years. Addition of chemotherapy did not affect the HRQoL outcomes. Also see section 7.5.4 for further discussion of QoL after TMT.

7.8.6 ***Non-curative or metastatic bladder cancer***

In patients with primary non-curative or metastastic disease HRQoL is reduced because of associated micturition problems, bleeding, pain and therefore disturbance of social and sexual life [564]. Beneficial impact of palliative surgery [565], RT [566], and/or chemotherapy on bladder-related symptoms have been described [567].

A HRQoL analysis was performed in platinum-refractory patients who were randomised to pembrolizumab vs. another line of chemotherapy (KEYNOTE-45 trial) [568]. It was reported that patients treated with pembrolizumab had stable or improved global health status/QoL, whereas those treated with investigators' choice of chemotherapy experienced declines in global health [568].

Recently, HRQoL data was presented from cohort 1 of the EV-201 study including 125 patients treated with enfortumab vedotin after failing previous treatment with platinum chemotherapy and anti–PD-1/L1 therapy [569]. Patients who remained on enfortumab vedotin treatment showed no detoriation in HRQoL. In patients with bone metastases at baseline, pain control and possibly pain reduction was observed.

7.8.7 Summary of evidence and recommendations for health-related quality of life

Summary of evidence	LE
Compared to non-cancer controls, the diagnosis and treatment of BC has a negative impact on HRQoL.	2a
There is no distinct difference in overall QoL between patients with continent or incontinent diversion.	1b
In patients with MIBC treated with RC, overall HRQoL declines immediately after treatment and recovers to baseline at 12 months post-operatively in most patients.	1b
In patients with MIBC treated with RT, overall HRQoL declines immediately after treatment, and recovers to baseline at 6 months post-treatment.	1b
HRQoL data are comparable for RARC (with either intracorporeal or extracorporeal urinary diversion) and ORC.	1b
In patients with MIBC treated with RT, concomitant chemotherapy or neo-adjuvant chemotherapy has no significant impact on HRQoL.	1b
Adjuvant treatment with nivolumab does not result in a clinically meaningful decrease in HRQoL compared to placebo.	1b
In patients with platinum-refractory advanced UC, pembrolizumab may be superior in terms of HRQoL compared to another line of chemotherapy.	1b

Recommendations	Strength rating
Use validated questionnaires to assess health-related quality of life in patients with muscle-invasive bladder cancer, both at baseline and post-treatment.	Strong
Discuss the type of urinary diversion taking into account a patient preference, existing comorbidities, tumour variables and coping abilities.	Strong

8. FOLLOW-UP

8.1 Follow-up in muscle invasive bladder cancer

An appropriate schedule for disease monitoring should be based on natural timing of recurrence; probability and site of recurrence; functional monitoring after urinary diversion and the potential available management options [570].

Nomograms on CSS following RC have been developed and externally validated, but their wider use cannot be recommended until further data become available [571, 572].

Current surveillance protocols are based on patterns of recurrence drawn from retrospective series only. Combining this data is not possible since most retrospective studies use different follow-up regimens and imaging techniques. Additionally, reports of asymptomatic recurrences diagnosed during routine oncological follow-up and results from retrospective studies are contradictory [573-575]. From the Volkmer B, *et al.*, series of 1,270 RC patients, no differences in OS were observed between asymptomatic and symptomatic recurrences [574]. Conversely, in the Giannarini, *et al.*, series of 479 patients; those with recurrences detected during routine follow-up (especially in the lungs) and with secondary urothelial tumours as the site of recurrence, had a slightly higher survival [573]. Boorjian, *et al.*, included 1,599 RC patients in their series, with 77% symptomatic recurrences. On multivariate analysis, patients who were symptomatic at recurrence had a 60% increased risk of death as compared to asymptomatic patients [575].

However, at this time, no data from prospective trials demonstrating the potential benefit of early detection of recurrent disease and its impact on OS are available [576].

8.2 Site of recurrence

8.2.1 Local recurrence

Local recurrence takes place in the soft tissues of the original surgical site or in LNs. Contemporary cystectomy has a 5–15% probability of pelvic recurrence which usually occurs during the first 24 months, most often within 6 to 18 months after surgery. However, late recurrences can occur up to five years after RC. Risk factors described are pathological stage, LNs, positive margins, extent of LND and peri-operative chemotherapy [577].

Patients generally have a poor prognosis after pelvic recurrence. Even with treatment, median survival ranges from four to eight months following diagnosis. Definitive therapy can prolong survival, but mostly provides significant palliation of symptoms. Trimodality management generally involves a combination of chemotherapy, radiation and surgery [576].

*8.2.2 **Distant recurrence***

Distant recurrence is seen in up to 50% of patients treated with RC for MIBC. As with local recurrence, pathological stage and nodal involvement are risk factors [578]. Systemic recurrence is more common in locally-advanced disease (pT3/4), ranging from 32 to 62%, and in patients with LN involvement (range 52–70%) [579].

The most likely sites for distant recurrence are LNs, lungs, liver and bone. Nearly 90% of distant recurrences appear within the first three years after RC, mainly in the first two years, although late recurrence has been described after more than 10 years. Median survival of patients with progressive disease treated with platinum-based chemotherapy is 9–26 months [580-582]. However, longer survival (28–33% at 5 years) has been reported in patients with minimal metastatic disease undergoing TMT management, including metastasectomy [324, 583].

*8.2.3 **Urothelial recurrences***

After RC, the incidence of new urethral tumours was 4.4% (1.3–13.7%). Risk factors for secondary urethral tumours are urethral malignancy in the prostatic urethra/prostate (in men) and bladder neck (in women). Orthotopic neobladder was associated with a significant lower risk of urethral tumours after RC (OR: 0.44) [584].

There is limited data, and agreement, about urethral follow-up, with some authors recommending routine surveillance with urethral wash and urine cytology and others doubting the need for routine urethral surveillance. 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 [576]. Treatment is influenced by local stage and grade of urethral occurrence. In urethral CIS, BCG instillations have success rates of 83% [585]. In invasive disease, urethrectomy should be performed if the urethra is the only site of disease; in case of distant disease, systemic chemotherapy is indicated [3].

Upper urinary tract UCs occur in 4–10% of cases and represent the most common sites of late recurrence (3-year DFS following RC) [586]. Median OS is 10–55 months, and 60–67% of patients die of metastatic disease [576]. A meta-analysis found that 38% of UTUC recurrence was diagnosed by follow-up investigations, whereas in the remaining 62%, diagnosis was based on symptoms. When urine cytology was used during surveillance, the rate of primary detection was 7% vs. 29.6% with UUT imaging. The meta-analysis concluded that patients with non-invasive cancer are twice as likely to have UTUC as patients with invasive disease [587]. Multifocality increases the risk of recurrence by three-fold, while positive ureteral or urethral margins increase the risk by seven-fold. Radical nephroureterectomy can prolong survival [588].

8.3 Time schedule for surveillance

Although, based on low level evidence only, some follow-up schedules have been suggested, guided by the principle that recurrences tend to occur within the first years following initial treatment. A schedule suggested by the EAU Guidelines Panel includes a CT scan (every 6 months) until the third year, followed by annual imaging thereafter. Patients with multifocal disease, NMIBC with CIS or positive ureteral margins are at higher risk of developing UTUC, which can develop late (> 3 years). In those cases, monitoring of the UUT is mandatory during follow-up. Computed tomography is to be used for imaging of the UUT [587].

The exact time to stop follow-up is not well known and recently a risk-adapted schedule has been proposed, based on the interaction between recurrence risk and competing health factors that could lead to individualised recommendations and may increase recurrence detection. Elderly and very low-risk patients (those with NMIBC or pT0 disease at final cystectomy report) showed a higher competing risk of non-BC mortality when compared with their level of BC recurrence risk. On the other hand, patients with locally-advanced disease or LN involvement are at a higher risk of recurrence for more than 20 years [589]. However, this model has not been validated, does not differentiate between pure UC or variant histologies, and does not incorporate several risk factors related to non-BC mortality. Subtype tumours (including urothelial subtypes, non-urothelial subtypes, and mixed subtypes) might be associated with a greater recurrence risk than pure UC. Recently, a different follow-up scheme for patients with subtype tumours has been proposed [590]. In case of pT0 patients with previous subtype in TURB or in those in the age range between 60 and 79 years, the follow-up should be longer than in pure UC since the risk of recurrence persists over time. Similar to pure UC, patients older than 80 years with subtype tumours might not need oncologic surveillance given the higher risk of non-BC mortality compared to the risk of recurrence whereas patients younger than 60 years should be offered extended surveillance (> 10

years) since the risk of recurrence will exceed that of non-BC mortality [590]. Future prospective studies are needed to answer the question whether a more intense follow- up for subtypes should be considered.

Furthermore, the prognostic implications of the different sites of recurrence should be considered. Local and systemic recurrences have a poor prognosis and early detection of the disease will not influence survival [591]. Despite this, the rationale for a risk-adapted schedule for BC surveillance appears to be promising and deserves further investigation.

Since data for follow-up strategies are sparse, a number of key questions were included in a recently held consensus project [81, 82]. Outcomes for all statements for which consensus was achieved are listed in Section 8.6.

8.4 Follow-up of functional outcomes and complications

Apart from oncological surveillance, patients with a urinary diversion need functional follow-up. Complications related to urinary diversion are detected in 45% of patients during the first five years of follow-up. In a series of 131 patients, this rate increased to 94% in those surviving > 15 years [592].

General functional complications are diverse and include: vitamin B12 deficiency, metabolic acidosis, worsening of renal function, urinary infections, urolithiasis and ureteroenteric stricture [593]. Benign ureteroenteric strictures may occur in up to 20% of patients [593]. Based on SEER data, cystectomy was found to be associated with a 21% increased risk of fractures compared to no RC due to chronic metabolic acidosis and subsequent long-term bone loss [591]. Since low vitamin B12 levels have been reported in 17% of patients with bowel diversion, in case of cystectomy and bowel diversion, vitamin B12 levels should be measured annually [81, 82, 594]. In a series of 3,360 patients who underwent RC for MIBC, 29% progressed to advanced chronic kidney disease within 12 months [595].

In a retrospective study comparing various forms of intestinal diversion, ileal conduits had fewer late complications than continent abdominal pouches or orthotopic neobladders [594]. The main long-term complications in ileal conduit patients are stomal complications in up to 24% and functional and/or morphological changes of the UUT in up to 30% of patients [594, 596, 597]. At 15 years of follow-up, 50% of patients developed UUT changes and 38% developed urolithiasis [598].

The main specific complications in patients with a neobladder are continence problems and emptying dysfunction [576]. Clifford *et al.*, prospectively evaluated continence outcomes in male patients undergoing orthotopic neobladder diversion [599]. Day-time continence increased from 59% at less than three months post-operatively to 92% after 12 to 18 months. Night-time continence increased from 28% at less than three months post-operatively to 51% after 18 to 36 months. Also of interest is the urinary bother in females with an orthotopic neobladder. Bartsch and co-workers reported day-time and night-time continence rates of 70.4% and 64.8%, respectively, in 56 female neobladder patients. Emptying disfunction is especially common in women: approximately two-thirds need to catheterise their neobladder, while almost 45% do not void spontaneously at all [600]. There seems to be a correlation between voiding patterns and nerve preservation; in 66 women bilateral preservation of autonomic nerves decreased the need for catheterisation to between 3.4–18.7% (CI: 95%) [601].

In a single-centre series of 259 male patients, long-term follow-up after orthotopic bladder substitution (median 121 months [range 60–267]), showed that excellent long-term functional outcomes can be achieved in high-volume centres with dedicated teams [602].

8.5 Summary of evidence and recommendations for specific recurrence sites

Site of recurrence	Summary of evidence	Recommendation	Strength rating
Local recurrence	Poor prognosis. Treatment should be individualised depending on the local extent of tumour.	Offer radiotherapy, chemotherapy and possibly surgery as options for treatment, either alone or in combination.	Strong
Distant recurrence	Poor prognosis.	Offer chemotherapy as the first option, and consider metastasectomy or radiotherapy in case of unique metastasis site.	Strong
Upper urinary tract recurrence	Risk factors are multifocal disease, NMIBC/CIS or positive ureteral margins.	See EAU Guidelines on Upper Urinary Tract Urothelial Carcinomas [1].	Strong
Secondary urethral tumour	Staging and treatment should be done as for primary urethral tumour.	See EAU Guidelines on Primary Urethral Carcinoma [3].	Strong

8.6 EAU-ESMO consensus statements on the management of advanced- and variant bladder cancer [81, 82]*

Consensus statement
After radical cystectomy with curative intent, regular follow-up is needed.
After radical cystectomy with curative intent, follow-up for the detection of second cancers in the urothelium is recommended.
After radical cystectomy with curative intent, follow-up of the urethra with cytology and/or cystoscopy is recommended in selected patients (e.g., multifocality, carcinoma *in situ* and tumour in the prostatic urethra).
After trimodality treatment with curative intent, follow-up for the detection of relapse is recommended every 3–4 months initially; then after 3 years, every 6 months in the majority of patients.
After trimodality treatment with curative intent, regular cystoscopic evaluation of the bladder wall is needed.
After trimodality treatment with curative intent, follow-up imaging with CT of thorax and abdomen to assess distant recurrence or recurrence outside the bladder is needed.
In patients with a partial or complete response after chemotherapy for metastatic urothelial cancer, regular follow-up is needed. Imaging studies may be done according to signs/symptoms.
In patients treated with radical cystectomy with curative intent and who have a neobladder, management of acid bases household includes regular measurements of pH and sodium bicarbonate substitution according to the measured value.
To detect relapse after radical cystectomy with curative intent, a CT of the thorax and abdomen is recommended up to five years post-operatively.
Vitamin B12 levels have to be measured annually in the follow-up of patients treated with radical cystectomy and bowel diversion with curative intent.

**Only statements which met the a priori consensus threshold across all three stakeholder groups are listed (defined as ≥ 70% agreement and ≤ 15% disagreement, or vice versa).*
CT = computed tomography.

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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: https://uroweb.org/guidelines/muscle-invasive-and-metastatic-bladder-cancer/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.

11. CITATION INFORMATION

The format in which to cite the EAU Guidelines will vary depending on the style guide of the journal in which the citation appears. Accordingly, the number of authors or whether, for instance, to include the publisher, location, or an ISBN number may vary.

The compilation of the complete Guidelines should be referenced as:
EAU Guidelines. Edn. presented at the EAU Annual Congress Paris 2024. ISBN 978-94-92671-23-3.

If a publisher and/or location is required, include:
EAU Guidelines Office, Arnhem, The Netherlands. http://uroweb.org/guidelines/compilations-of-all-guidelines/

References to individual guidelines should be structured in the following way:
Contributors' names. Title of resource. Publication type. ISBN. Publisher and publisher location, year.

EAU Guidelines on

Upper Urinary Tract Urothelial Carcinoma

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1. INTRODUCTION

1.1 Aim and scope

This overview represents the updated European Association of Urology (EAU) Guidelines for the management of upper urinary tract urothelial carcinoma (UTUC). Separate EAU guidelines are available addressing non-muscle-invasive bladder cancer [1], muscle-invasive and metastatic bladder cancer (MIBC) [2], and primary urethral carcinoma [3].

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

1.2 Panel composition

The European Association of Urology (EAU) Guidelines Panel on NMIBC consists of an international multidisciplinary group of clinicians, including urologists, uro-oncologists, a radiologist, a pathologist, and a patient representative. Members of this panel have been selected based on their expertise and to represent the professionals treating patients suspected of harbouring urothelial carcinoma (UC). All 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/guidelines/upper-urinary-tract-urothelial-cell-carcinoma/panel/.

1.3 Available publications

A quick reference document, the Pocket Guidelines is available online and in print. This is an abridged version which may require consultation together with the full text version. Several scientific publications are available, the most recent scientific summary was published in 2021 [4]. All documents are accessible through the EAU website: https://uroweb.org/guideline/upper-urinary-tract-urothelial-cell-carcinoma/.

1.4 Publication history & summary of changes

The first EAU Guidelines on UTUC were first published in 2011. Standard procedure for EAU Guidelines includes an annual assessment of newly published literature in the field to guide future updates. The 2024 UTUC Guidelines presents an update of the 2023 version.

1.4.1 Summary of changes

For the 2024 UTUC Guidelines, new and relevant evidence was identified, collated and appraised through a structured assessment of the literature for all sections of the Guidelines. Key changes include the addition of:

- New text and guidelines updates in section 3.2.2 on the genetic risk factors and the implications of identifying lynch syndrome's related UTUCs, and in section 3.4 on the molecular background of UTUCs;
- new text updates in section 6.1.2.2 on tumour location, multifocality, size and hydronephrosis;
- updates in section 6.2 on the risk stratification for clinical decision making, both in text and evidence;
- key updates to the text, evidence and guidelines in section 7.3.2 on the management of distant metastases.

2. METHODS

2.1 Data identification

For the 2023 UTUC Guidelines, new and relevant evidence has been identified, collated, and appraised through a structured assessment of the literature. The search was restricted to articles published between May 4th 2022 and May 1st 2023. Databases searched included Pubmed, Ovid, EMBASE and both the Cochrane Central Register of Controlled Trials and the Cochrane Database of Systematic Reviews. After deduplication, a total of 333 unique records were identified, retrieved, and screened for relevance.

Excluded from the search were basic research studies, case series, reports, and editorial comments. The publications identified were mainly retrospective, including some large multicentre studies. Owing to the scarcity of randomised data, articles were selected based on the following criteria: evolution of concepts, intermediate- and long-term clinical outcomes, study quality, and relevance. Older studies were only included if they were historically relevant.

A detailed search strategy is available online: https://uroweb.org/guideline/upper-urinary-tract-urothelial-cell-carcinoma/?type=appendicespublications.

Recommendations within the Guidelines are developed by the panels to prioritise clinically important care decisions. The strength of each recommendation is determined by the balance between desirable and undesirable consequences of alternative management strategies, the quality of the evidence (including certainty of estimates), and the nature and variability of patient values and preferences. This decision process, which can be reviewed in the strength rating forms which accompany each guideline statement, addresses a number of key elements:

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

Strong recommendations typically indicate a high degree of evidence quality and / or a favourable balance of benefit to harm and patient preference. Weak recommendations typically indicate availability of lower quality evidence, and/or equivocal balance between benefit and harm, and uncertainty or variability of patient preference [6].

Additional methodology information and a list of associations endorsing the EAU Guidelines can be found in the online: https://uroweb.org/eau-guidelines/methodology-policies.

2.2 Review

The UTUC Guidelines was subject to peer-reviewed prior to publication in 2023.

3. EPIDEMIOLOGY, AETIOLOGY AND PATHOLOGY

3.1 Epidemiology

Urothelial carcinoma (UC) is the second most common urological malignancy in developed countries [7]. They can be localised in the lower (bladder and urethra) and/or the upper (pyelocaliceal cavities and ureter) urinary tract. Bladder cancer (BC) accounts for 90–95% of UCs whilst upper tract urothelial carcinomas (UTUC) account for only 5–10% of UCs with an estimated annual incidence in Western countries of almost two cases per 100,000 inhabitants [1]. This rate has risen in the past few decades likely as a result of improved detection and the aging population [8, 9].

The peak incidence is in individuals aged 70–90 years and UTUC is twice as common in men [10]. A retrospective international registry including data from 2,380 patients diagnosed between 2014 and 2019 (101 centres from 29 countries) confirmed that UTUC patients were predominantly male (70.5%) and 53.3% were past or present smokers. The majority of patients (53%) were diagnosed after they presented with symptoms, mainly visible haematuria [11]. This was confirmed by a meta-analysis pooling 44 studies that showed a pooled UTUC incidence rate of 0.75% in patients with visible haematuria and 0.17% for those with non-visible haematuria [12]. In addition, approximately two-thirds of patients who present with UTUCs have muscle-invasive disease at diagnosis compared to 15–25% of patients diagnosed with *de novo* BC [13]. The higher incidence of muscle-invasive disease in UTUC vs. BC has been confirmed in population-based studies from Germany and England suggesting that muscle-invasive UTUC represents approximately half of incident cases in recent years [14, 15]. Approximately 9% of patients present with metastasis [8, 16-18].

Pyelocaliceal tumours are approximately twice as common as ureteral tumours and multifocal tumours are found in approximately 10–20% of cases [19]. The presence of concomitant carcinoma *in situ* of the upper tract is between 11% and 36% [8]. In 17% of cases, concurrent BC is present [20] whilst a prior history of BC is found in 41% of American men but in only 4% of Chinese men [21]. This, along with genetic and epigenetic factors, may explain why Asian patients present with more advanced and higher-grade disease compared to other ethnic groups [8].

Following treatment, recurrence in the bladder occurs in 29% of UTUC patients, depending on patient-, tumour- and treatment-specific characteristics [22] compared to a 2–5% recurrence rate in the contralateral upper tract [23].

Upper tract UC and BC exhibit significant differences in the prevalence of common genomic alterations. In individual patients with a history of both tumours, BC and UTUC are often clonally related. Genomic characterisation of UTUC provides information regarding the risk of bladder recurrence and can identify tumours associated with Lynch syndrome [24].

Regarding UTUC occurring in patients with BC, of 82 patients treated with intravesical bacillus Calmette-Guérin (BCG) for high-risk BC who had regular upper tract imaging between years 1 and 3, 13% developed UTUC, all of which were asymptomatic [25], whilst in another series of 307 patients without routine upper tract imaging the incidence of UTUC after BC was 25% [26]. A multicentre cohort study (n = 402) with a 50 month follow-up demonstrated a UTUC incidence of 7.5% in NMIBC patients receiving BCG with predictors being intravesical recurrence and non-papillary tumour at transurethral resection of the bladder (TURB) [27]. Following radical cystectomy for MIBC, 3–5% of patients develop a metachronous UTUC [28, 29].

3.2 Risk factors

*3.2.1 **Environmental risk factors***

A number of environmental risk factors have been implicated in the development of UTUC [19, 30]. Published evidence in support of a causative role for these factors is not strong, with the exception of smoking and aristolochic acid. Tobacco exposure increases the relative risk of developing UTUC by 2.5 to 7.0 fold [31-33]. A large population-based study assessing familial clustering in relatives of UC patients, including 229,251 relatives of case subjects and 1,197,552 relatives of matched control subjects, has demonstrated genetic or environmental roots independent of smoking-related behaviours. With more than 9% of the cohort being UTUC patients, clustering was not seen for UTUC. This suggests that the familial clustering of UC is specific to the lower urinary tract (i.e., BC) [34].

Aristolochic acid, a nitrophenanthrene carboxylic acid produced by aristolochia plants, which are used worldwide for different health-related issues, especially in China and Taiwan [35], exerts negative effects on the urinary system. Aristolochic acid irreversibly injures renal proximal tubules resulting in chronic tubulointerstitial disease, while the mutagenic properties of this carcinogen can lead to UTUC [35-37]. Aristolochic acid has been linked to BC, renal cell carcinoma, hepatocellular carcinoma, and intrahepatic cholangiocarcinoma [38]. Two routes of exposure to aristolochic acid are known: (i) environmental contamination of agricultural products by aristolochia plants, as reported for Balkan endemic nephropathy [39]; and (ii) ingestion of aristolochia-based herbal remedies [40, 41]. Following bioactivation, aristolochic acid reacts with genomic DNA to form aristolactam-deoxyadenosine adducts [42]; these lesions persist for decades in target tissues, serving as robust biomarkers of exposure [43]. These adducts generate a unique mutational spectrum, characterised by A>T transversions located predominately on the non-transcribed strand of DNA [38, 44]. However, it is estimated that less than 10% of individuals exposed to aristolochic acid develop UTUC [37].

Two retrospective series demonstrated that aristolochic acid-associated UTUC is more common in females [45, 46]. However, females with aristolochic acid UTUC have a better prognosis than their male counterparts. Consumption of arsenic in drinking water and aristolochia-based herbal remedies together appears to have an additive carcinogenic effect [47]. In Taiwan and Chile, the presence of arsenic in drinking water has been tentatively linked to UTUC [48, 49].

In addition, alcohol consumption may be associated with development of UTUC. A large case-control study (1,569 cases and 506,797 controls) has evidenced a significantly higher risk of UTUC in ever-drinkers compared to never-drinkers (OR: 1.23; 95% CI: 1.08–1.40, p = 0.001). Compared to never-drinkers, the risk threshold for UTUC was > 15 g of alcohol/day. A dose-response has been observed [50].

*3.2.2 **Genetic risk factors***

Lynch syndrome is characterised by a predisposition to early onset colorectal cancer and several extra-colonic malignancies related to pathogenic germline mutations in one allele of the mismatch repair (MMR) genes MLH1, MSH2, MSH6 or PMS2. After colorectal and endometrial cancers, UTUC is the 3rd most common malignancy in the Lynch syndrome spectrum [51]. Identifying Lynch Syndrome's related UTUCs has important clinical implications for both the patient and their relatives given the high risk of developing subsequent multiple different malignancies in the carrier and the strong hereditary predisposition of this condition. Germline mutations in MMR genes are found in 9% of patients with UTUC compared to 1% of patients with BC [52].

From a genetic perspective, the majority of tumours develop in MSH2 and MSH6 mutation carriers [53]. The carcinogenesis is related to the somatic mutation of the second allele of the germline-mutated MMR gene. This will result in a deficient MMR (dMMR) system related to the loss of the expression of the corresponding protein MLH1, MSH2, MSH6 or PMS2 in immunochemistry, which can be responsible for a microsatellite instability identified using the PCR method.

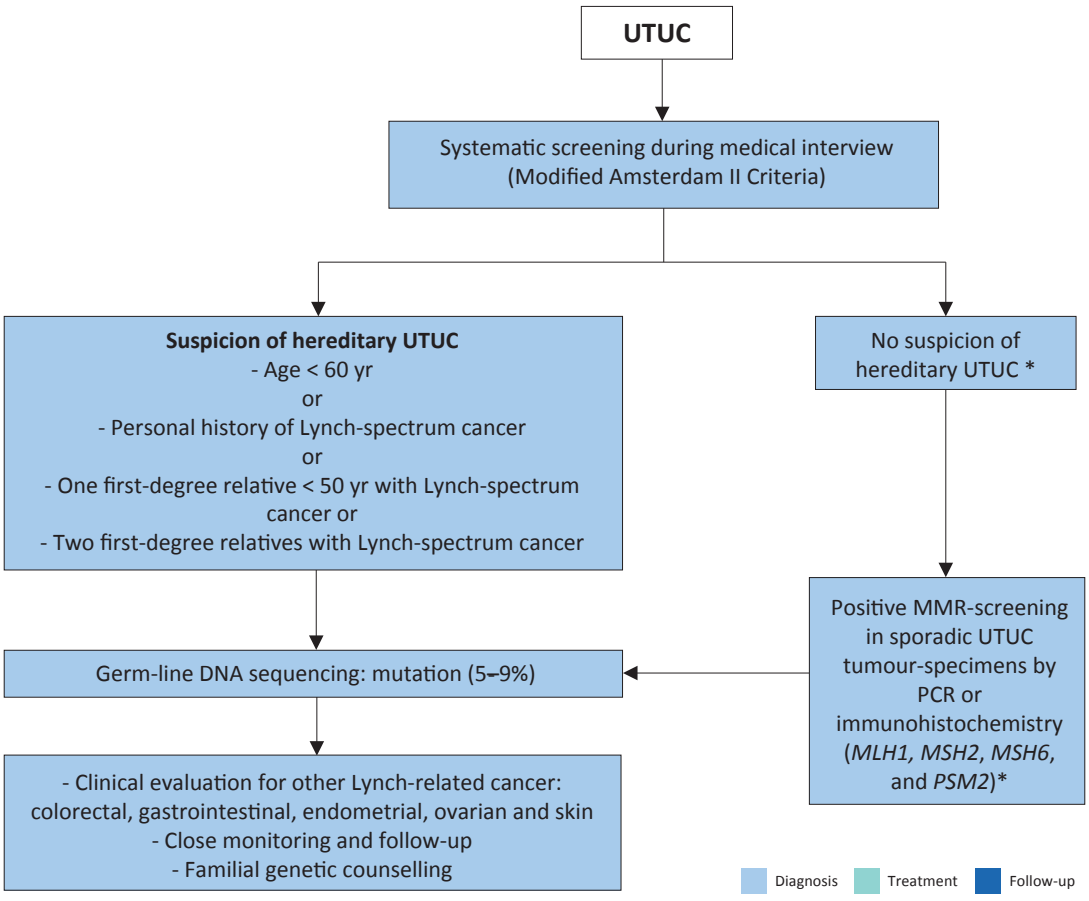
From a clinical perspective, although the PREMM5 model has been developed to estimate the cumulative probability of an individual to carry a germline mutation related to the Lynch syndrome [54], the Amsterdam II criteria remains predominantly used to identify families that are at increased risk of Lynch syndrome [55]. The latter include:

1. At least three relatives with a Lynch-associated cancer (colorectal, endometrium, small bowel or UTUC);
2. A first degree relative to the other two;
3. At least two successive affected generations;
4. At least one relative diagnosed before the age 50;
5. Exclusion of familial adenomatous polyposis in the colorectal cancer cases;
6. Pathological confirmation of the diagnosis.

A study of 115 consecutive UTUC patients reported that 13.9% screened positive for potential Lynch syndrome using the Amsterdam II criteria and 5.2% had confirmed Lynch syndrome [56].

Another UTUC-specific study has suggested that an age <60 at initial diagnosis and a personal history of any other Lynch-related malignancy could be both associated with an increased risk of Lynch syndrome in these patients [57]. A simplified screening tool for UTUC patients has been proposed including these two criteria associated with two others deriving from the Amsterdam II criteria and including one-first degree relative with Lynch-related cancer diagnosed before 50 and two first-degree relatives with Lynch-related cancer regardless of age [58]. Using this simplified screening tool, the proportion of UTUC patients with a suspicion of Lynch-related disease could be more than 20% [58]. Importantly, patients with UTUC who are identified at high risk for Lynch syndrome based on clinical criteria should undergo germline DNA sequencing and family counselling [59, 60] (Figure 3.1). Nonetheless, given the limited diagnostic performance of clinical criteria, UTUC patients without suspicion for genetic predisposing factors could be tested for MSI or dMMR using PCR or immunochemistry, respectively. As for any clinical suspicion of hereditary UTUC, those with positive test should also undergo germline DNA sequencing and family counselling [52, 61-64] (Figure 3.1).

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



**These patients may benefit from MMR deficiency screening using PCR or IHC. Positive result should prompt subsequent testing for germline DNA sequencing mutations.*
MMR = mismatch repair; mismatch repair genes = MLH1, MSH2, MSH6, and PSM2; UTUC = upper urinary tract urothelial carcinoma.

Other germline mutations in MSH2, BRCA2, BRCA1 and BRIP1 has been shown to significantly increase the risk of developing UTUC in Chinese patients [65]. Differences in the exposure and susceptibility to carcinogens such as smoking may explain the differences in susceptibility to genetic predisposing mutations to overt disease. Some genetic polymorphisms are associated with an increased risk of cancer or faster disease progression that introduces variability in the inter-individual susceptibility to the risk factors previously mentioned. Upper urinary tract UCs may also share some risk factors and described molecular pathways with bladder UC [24]. So far, two UTUC-specific polymorphisms have been reported [66].

3.2.3 History of bladder cancer

A history of BC is associated with a higher risk of developing UTUCs (see Section 3.1). Patients requiring ureteral stenting at the time of TURB, including prior to radical cystectomy, have been shown to have a higher risk for upper tract recurrence [67, 68].

3.3 Histology and classification

3.3.1 Histological types

Upper urinary tract tumours are almost always UCs with pure non-urothelial histology being rare [69, 70]. However, histological subtypes are present in approximately 25% of UTUCs [71, 72]. Pure squamous cell carcinoma of the urinary tract is often assumed to be associated with chronic inflammatory diseases and infections arising from urolithiasis [73, 74]. Urothelial carcinoma with divergent squamous differentiation (i.e., squamous subtype) is present in approximately 15% of cases [73]. Keratinising squamous metaplasia of urothelium is a risk factor for squamous cell cancers and therefore mandates surveillance. Upper urinary tract UCs with different subtypes are high- grade and have a worse prognosis compared to pure UC [72, 75, 76]. Other subtypes, although rare, include sarcomatoid with inverted growth also being is frequent in the UUT [76, 77].

Collecting duct carcinomas, which may seem to share similar characteristics with UCs, display a unique transcriptomic signature similar to renal cancer, with a putative cell of origin in the distal convoluted tubules. Therefore, collecting duct carcinomas are considered as renal tumours [78].

3.4 Molecular background of UTUCs

A number of studies focusing on molecular classification have been able to demonstrate genetically distinct groups of UTUC by evaluating DNA, RNA and protein expression. The most common genomic alterations included FGFR3, chromatin remodelling genes (i.e., KMT2D and KDM6A), TP53/MDM2, and other typical tumour suppressors/oncogenes such as CDKN2A or RAS [79]. Low-grade tumours are enriched for activating FGFR3 mutations (> 90% tumours) and depleted of TP53/MDM2 mutations, whereas high-grade tumours often show mutations in TP53 signalling [80]. It has also been shown that UTUC has a T-cell depleted immune contexture and activated FGFR3 signalling [81]. Five different molecular subtypes with different gene expression, tumour location and outcome have been identified, but, as yet, it is unclear whether these subtypes will respond differently to treatment and therefore, these subtypes have limited use in daily practice [82].

3.5 Summary of evidence and recommendations for epidemiology, aetiology, and histology

Summary of evidence	LE
Aristolochic acid and smoking exposure increases the risk for UTUC.	2a
Patients with Lynch syndrome are at risk for UTUC.	2a

Recommendations	Strength rating
Evaluate patient and family history to screen patients for Lynch syndrome using modified Amsterdam II criteria.	Strong
Perform germline DNA sequencing in patients with clinical suspicion of hereditary UTUC.	Weak
Offer testing for MMR proteins or microsatellite instability in patients without clinical suspicion of hereditary UTUC.	Weak

4. STAGING AND CLASSIFICATION SYSTEMS

4.1 Classification

The classification and morphology of UTUC and BC are similar [1]. However because of the difficulty in adequate sample acquisition, it is often difficult to distinguish between non-invasive papillary tumours [83], flat lesions (carcinoma *in situ* [CIS]), and invasive carcinoma in biopsies. Therefore, histological grade is often used for clinical decision making as it is strongly associated with pathological stage [84].

4.2 Tumour Node Metastasis staging

The tumour, node, metastasis (TNM) classification is shown in Table 1 [85]. The regional lymph nodes (LNs) are the hilar and retroperitoneal nodes and, for the mid- and distal ureter, the pelvic nodes. Laterality does not affect N classification.

4.3 Tumour grade

In 2004 and 2016, the WHO and the International Society of Urological Pathology published a new histological classification of UCs which provides a different patient stratification between individual categories compared to the older 1973 WHO classification [86, 87]. In 2022, an update of the 2004/2016 WHO grading classification was published without major changes [88]. These guidelines are still based on both the 1973 and 2004/2016 WHO classifications since most published data use the 1973 classification [83].

Table 1: TNM classification 2017 for upper tract urothelial cell carcinoma [85]

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 muscularis
T3	(Renal pelvis) Tumour invades beyond muscularis into peripelvic fat or renal parenchyma (Ureter) Tumour invades beyond muscularis into periureteric fat
T4	Tumour invades adjacent organs or through the kidney into perinephric fat
N - Regional lymph nodes	
NX	Regional lymph nodes cannot be assessed
N0	No regional lymph node metastasis
N1	Metastasis in a single lymph node 2 cm or less in the greatest dimension
N2	Metastasis in a single lymph node more than 2 cm, or multiple lymph nodes
M - Distant metastasis	
M0	No distant metastasis
M1	Distant metastasis

TNM = Tumour, Node, Metastasis (classification).

5. DIAGNOSIS

5.1 Symptoms

The diagnosis of UTUC may be incidental or symptom related. Flank pain, due to clot or tumour tissue obstruction can occur in 20–32% of cases [11]. Systemic symptoms (including anorexia, weight loss, malaise, fatigue, fever, night sweats, and cough) in patients with UTUC should prompt evaluation for metastases associated with a worse prognosis [11]. Symptoms at diagnosis are associated with indicate a worse prognosis [89].

5.2 Imaging

*5.2.1 **Computed tomography***

Computed tomography (CT) urography has the highest diagnostic accuracy of the available imaging techniques [90]. A meta-analysis of 13 studies comprising 1,233 patients revealed a pooled sensitivity of CT urography for UTUC of 92% (CI: 0.85–0.96) and a pooled specificity of 95% (CI: 0.88–0.98) [91].

Rapid acquisition of thin sections allows high-resolution isotropic images that can be viewed in multiple planes to assist with diagnosis without loss of resolution. Epithelial "flat lesions" without mass effect or urothelial thickening are generally not visible with CT.

The presence of enlarged LNs on CT is highly predictive of metastases in UTUC [92, 93].

*5.2.2 **Magnetic resonance urography***

Magnetic resonance (MR) urography is indicated in patients who cannot undergo CT urography, usually when radiation or iodinated contrast media are contraindicated [94]. The sensitivity of MR urography is 75% after contrast injection for tumours < 2 cm [94]. Computed tomography urography is more sensitive and specific for the diagnosis and staging of UTUC compared to MR urography [95].

*5.2.3 **^{18}F-Fluorodeoxglucose positron emission tomography/computed tomography***

A retrospective multicentre publication on the use of 18F-Fluorodeoxglucose positron emission tomography/computed tomography (FDG-PET/CT) for the detection of nodal metastasis in 117 surgically-treated UTUC patients reported promising sensitivity and specificity of 82% and 84%, respectively. Suspicious LNs on FDG-PET/CT were associated with worse recurrence-free survival [96]. These results warrant further validation and comparison with MR and CT. FDG-PET can also be used to assess (nodal and distant) metastases in patients unfit for iodinated contrast media due to renal impairment or allergy.

5.3 Cystoscopy

Urethrocystoscopy is an integral part of UTUC work-up to rule out concomitant BC [8, 20].

5.4 Cytology and urinary markers

Abnormal cytology may indicate high-grade UTUC when bladder cystoscopy is normal, and in the absence of CIS in the bladder and prostatic urethra [1, 97]. Voided urine cytology is less sensitive for UTUC than selectively obtained cytology from the affected upper tract [98]. In a recent study, barbotage cytology detected up to 91% of cancers [99]. Barbotage cytology taken from the renal cavities and ureteral lumina is preferred before application of a contrast agent for retrograde ureteropyelography as it may cause deterioration of cytological specimens [97, 99]. Retrograde ureteropyelography remains an option to detect UTUCs [84, 100, 101]. The sensitivity of fluorescence *in situ* hybridisation (FISH) for molecular abnormalities characteristic of UTUCs is approximately 72–84% [102, 103]. In a systematic review, including 25 studies on cytology and urinary markers, cytology and FISH were most commonly used [104]. FISH had comparable specificity (80-100%) and a higher sensitivity (35-86%) compared to cytology (11-71%). However, considering the wide ranges in sensitivity and specificity for both cytology and FISH, the authors concluded that these test were suboptimal to rule out cancer/UTUC. A prospective study in 79 patients with suspicion of UTUC using upper tract urine collected just before URS, reported sensitivities for Xpert Bladder, FISH, Bladder Epicheck and cytology of 100%, 87%, 64% and 42% , respectively. Specificities were 4%, 82%, 79% and 94%, respectively [105]. FISH, Bladder Epicheck and cytology could be helpful as an ancillary tool to detect UTUC; however, further confirmation in well-designed prospective comparative trials is needed.

5.5 Diagnostic ureteroscopy

Flexible ureteroscopy (URS) is used when necessary to confirm the diagnosis of UTUC by visualising the ureter, renal pelvis and collecting system and perform a biopsy of suspicious lesions. It is also essential for meticulous tumour mapping before considering kidney-sparing options for UTUC. Presence, appearance, multifocality and size of the tumour can be determined using URS. In addition, ureteroscopic biopsies can determine tumour

grade in more than 90% of cases with a low false-negative rate, regardless of sample size [106]. However, undergrading occurs with ureteroscopic diagnostic biopsy compared to nephroureterectomy specimens [107], making second-look URS necessary, as part of follow-up if kidney-sparing treatment is chosen [84, 108, 109] .

Ureteroscopy also facilitates selective ureteral sampling for cytology [101, 110, 111]. Stage assessment using ureteroscopic biopsy can be inaccurate, hence, combining ureteroscopic biopsy grade, imaging findings, and urinary cytology may help in the decision-making process between radical nephroureterectomy (RNU) and kidney-sparing therapy [111, 112]. In a meta-analysis comparing URS vs. no URS prior to RNU, 8 out of 12 studies found an increased risk for intravesical recurrence in those undergoing URS [113]. Performing a biopsy at URS was also identified as a risk factor for intravesical recurrence [113]. A second systematic review of 16 studies showed that URS alone was not significantly related to intravesical recurrence; whereas URS with a biopsy significantly increased the risk for subsequent intravesical recurrence albeit without an impact on overall survival and non-urothelial recurrence [114]. This underlines the need for a study evaluating whether an immediate intravesical instillation of chemotherapy in patients who underwent URS plus biopsy, or laser treatment, for UTUC can lower the intravesical recurrence rate after RNU (see section 7.2.4.2).

Technical developments in flexible ureteroscopes and the use of novel imaging techniques may improve visualisation and diagnosis of flat lesions [115]. Narrow-band imaging is a promising technique, but results are preliminary [116]. Optical coherence tomography and confocal laser endomicroscopy (Cellvizio®) have been used *in vivo* to evaluate tumour grade and/or for staging purposes, with a promising correlation with definitive histology in high-grade UTUC [117, 118].

5.6 Summary of evidence and recommendations for the diagnosis of UTUC

Summary of evidence	LE
The diagnosis and staging of UTUC is best done with computed tomography urography and URS.	2a
Selective urinary cytology has high sensitivity in high-grade tumours, including carcinoma *in situ*.	3
Urethrocystoscopy can detect concomitant BC.	2a

Recommendations	Strength rating
Perform a urethrocystoscopy to rule out bladder tumour.	Strong
Perform chest, abdominal and pelvis with computed tomography (CT) urography for diagnosis and staging.	Strong
Use diagnostic ureteroscopy (URS) if imaging and voided urine cytology are not sufficient for the diagnosis and/or risk-stratification of patients suspected to have UTUC.	Strong
Magnetic resonance urography or ^{18}F-Fluorodeoxglucose positron emission tomography/CT may be used when CT is contra-indicated.	Weak

6. PROGNOSIS

6.1 Prognostic factors

Many prognostic factors have been identified and can be used to risk-stratify patients in order to decide on the most appropriate local treatment (radical vs. kidney-sparing) and discuss peri-operative systemic therapy. Factors can be divided into patient-related factors and tumour-related factors.

*6.1.1 **Patient-related factors***

6.1.1.1 Age and gender

Older age at the time of RNU is independently associated with decreased cancer-specific survival (CSS) [119, 120]. Gender has no impact on prognosis of UTUC [121].

6.1.1.2 Ethnicity

A multicentre study of international patients from various academic centres did not show any difference in outcomes between races [122]. In contrast, U.S. population-based studies have indicated that African-American patients have worse outcomes than other ethnicities. The cause of this difference is unclear, possibly being related to access to care and/or biological patterns. Another study has demonstrated differences between Chinese and American patients at presentation in terms of risk factors, disease characteristics and predictors of adverse oncologic outcomes [21].

6.1.1.3 Genetic pre-disposition

Patients who test positive for Lynch syndrome, are significantly younger and exhibit a higher prevalence of UTUC with for ureteral location [123]. No impact on prognosis has been shown to date.

6.1.1.4 Tobacco consumption

Being a smoker at diagnosis increases the risk for disease recurrence, mortality [124, 125] and intravesical recurrence after RNU [126]. Smoking cessation over ten years improves outcomes to the level of non-smokers [125, 127].

6.1.1.5 Surgical delay

A delay between diagnosis of an invasive tumour and its removal may increase the risk of disease progression. Once a decision regarding RNU has been made, the procedure should be carried out within twelve weeks, whereas a treatment delay below four weeks has been suggested for the subgroup of patients with ureteral UTUC [128-132].

6.1.1.6 Other factors

High comorbidity and performance indices scores (e.g. American Society of Anesthesiologists [ASA], performance status [PS], and Charlson Comorbidity Index) are also associated with worse survival outcomes across disease stages [133-136].

A higher ASA score confers worse CSS after RNU [137], as does poor PS [138]. Obesity and higher body mass index adversely affect cancer-specific outcomes in patients treated with RNU [139], with potential differences between races [140]. Several blood-based biomarkers have been associated with locally-advanced disease and cancer-specific mortality such as high pre-treatment-derived neutrophil- lymphocyte ratio [141-144], low albumin [143-145], high C-reactive protein [143] or modified Glasgow score [146], high De Ritis ratio (aspartate transaminase/alanine transaminase) [147], altered renal function [143, 148] and high fibrinogen [143, 148].

*6.1.2 **Tumour-related factors***

6.1.2.1 Tumour stage and grade

The main prognostic factors are tumour stage and grade [111, 120, 149, 150]. Upper urinary tract UCs that invade the muscle have a poor prognosis. In a large Dutch series of UTUC, 5-year CSS was 86% for non- muscle-invasive tumours, 70% for muscle-invasive organ-confined tumours and 44% for locally-advanced tumours [18]. A contemporary SEER analysis of RNUs for high-risk disease showed that 5-year CSS was 86% for T1N0, 77% for T2N0, 63% for T3N0 and 39% for T4N0/T any N1–3 [151]. pT3 sub staging (pT3a vs. pT3b) might be relevant [152]; however, high quality validation is lacking.

6.1.2.2 Tumour location, multifocality, size and hydronephrosis

6.1.2.2.1 Multifocality

Approximately 7-42% of UTUC patients have been reported to have multifocal tumours [153-157]. Patients with multifocal tumours are more likely to harbour advanced tumour stage and a worse prognosis despite treatment with RNU [153-157]. However, multifocal tumours can also have a good prognosis and be present in the setting of otherwise low-risk UTUC.

It is important to note that the definition of multifocality varies among studies. Some studies consider the number of lesions [156], while others focus on tumour location (i.e., both renal pelvis and ureter) [153-155, 157].

Taken together, tumour multifocality alone is insufficient for risk stratification, and a combination of factors is needed to determine whether kidney-sparing surgery is a safe option. Patients should be categorised as high-risk UTUC not only when tumour multifocality is present but when it is accompanied by high risk factors (see Figure 6.1).

6.1.2.2.2 Hydroureteronephrosis

Hydroureteronephrosis has been linked to advanced disease and poor prognosis in patients treated with RNU [92, 158, 159]. A recent meta-analysis of 22 studies involving 7,542 patients found pre-operative hydroureteronephrosis to be significantly associated with ureteral tumour location, advanced tumour stage, and lymph node metastasis [160]. In addition, pre-operative hydroureteronephrosis was independently associated with worse overall, cancer-specific, and disease-free survival, but not intravesical recurrence [160].

It is important to note that some low-risk UTUC patients may exhibit hydroureteronephrosis with for example a pTa low-grade tumour obstructing the ureter. Taken together, just like tumour multifocality, the presence of hydroureteronephrosis alone is insufficient for risk stratification, and a combination of factors is needed to determine whether kidney-sparing surgery is a safe option. Patients should be categorised as high-risk UTUC not only when pre-operative hydroureteronephrosis is present but if it is accompanied by other high risk factors (see Figure 6.1).

6.1.2.2.3 Tumour size

Increasing tumour size is linked to a higher risk of muscle-invasive and non-organ-confined disease in both ureteral and renal pelvis UTUC cases [161]. A recent meta-analysis of 32,292 patients confirmed that larger tumours are significantly associated with worse overall, cancer-specific, and disease-free survival, as well as intravesical recurrence [161]. In renal pelvis UTUC, where the median tumour size ranges from 3.5 to 4.0 cm, each 1 cm increase in tumour size elevates the risk of harbouring muscle-invasive disease at RNU by 1.25-fold [162]. A recent multi-institutional study with 932 patients suggested that a 2 cm tumour size serves as the optimal threshold for identifying high-risk patients (> pT2 UTUC) [163]. However, measuring tumour size lacks standardisation, leading to inter-assessor variability.

Taken together, just like tumour multifocality and hydroureteronephrosis, tumour size alone is insufficient for risk stratification, and a combination of factors is needed to determine whether kidney-sparing surgery is a safe option. Therefore, similar to tumour multifocality and hydroureteronephrosis, tumour size alone should not dictate therapeutic decisions. Patients should be categorised as high-risk UTUC not only when tumour size exceeds 2 cm but if it is accompanied by other high risk factors (see Figure 6.1).

6.1.2.3 Pathological subtypes

Pathological subtypes are associated with worse CSS and overall survival (OS) [72]. Most studied subtypes are micropapillary [75], squamous [164] and sarcomatoid [75], all of which are consistently associated with locally-advanced disease and worse outcome [73]. Patients harbouring pathological subtypes should be proposed RNU after a shared-decision process due to the higher risk of progression.

6.1.2.4 Lymph node involvement

Patients with nodal metastasis experience poor survival after surgery [165]. Lymph node density (cut-off 30%) and extranodal extension are powerful predictors of survival outcomes in N+ UTUC [166-168]. Lymph node dissection (LND) performed at the time of RNU allows for optimal tumour staging, although its curative role remains controversial [167, 169-172].

6.1.2.5 Lymphovascular invasion

Lymphovascular invasion (LVI) is present in approximately 20% of invasive UTUCs and is an independent predictor of survival [173-175]. Lymphovascular invasion status should be specifically reported in the pathological reports of all UTUC specimens [176, 177].

6.1.2.6 Surgical margins

Positive soft tissue surgical margin is associated with a higher risk of disease recurrence after RNU. Pathologists should look for and report positive margins at the level of ureteral transection, bladder cuff, and around the tumour [178].

6.1.2.7 Other pathological factors

Extensive tumour necrosis (> 10% of the tumour area) is an independent prognostic predictor in patients who undergo RNU [179]. Where neoadjuvant treatment was given, pathological downstaging is associated with better OS [180, 181]. The architecture of UTUC, as determined from pathological examination of RNU specimens, is also a strong prognosticator with sessile growth pattern being associated with worse outcome [182-184]. Concomitant CIS in organ-confined UTUC and a history of bladder CIS are associated with a higher risk of recurrence and cancer-specific mortality [185, 186]. Macroscopic infiltration or invasion of peri-pelvic adipose

tissue confers a higher risk of disease recurrence after RNU compared to microscopic infiltration of renal parenchyma [71, 187].

6.1.3 Molecular markers

Because of the rarity of UTUC, the main limitations of molecular studies are their retrospective design and, for most studies, small sample size. None of the investigated markers have been validated to support their introduction in daily clinical decision making [79, 143].

6.2 Risk stratification for clinical decision making

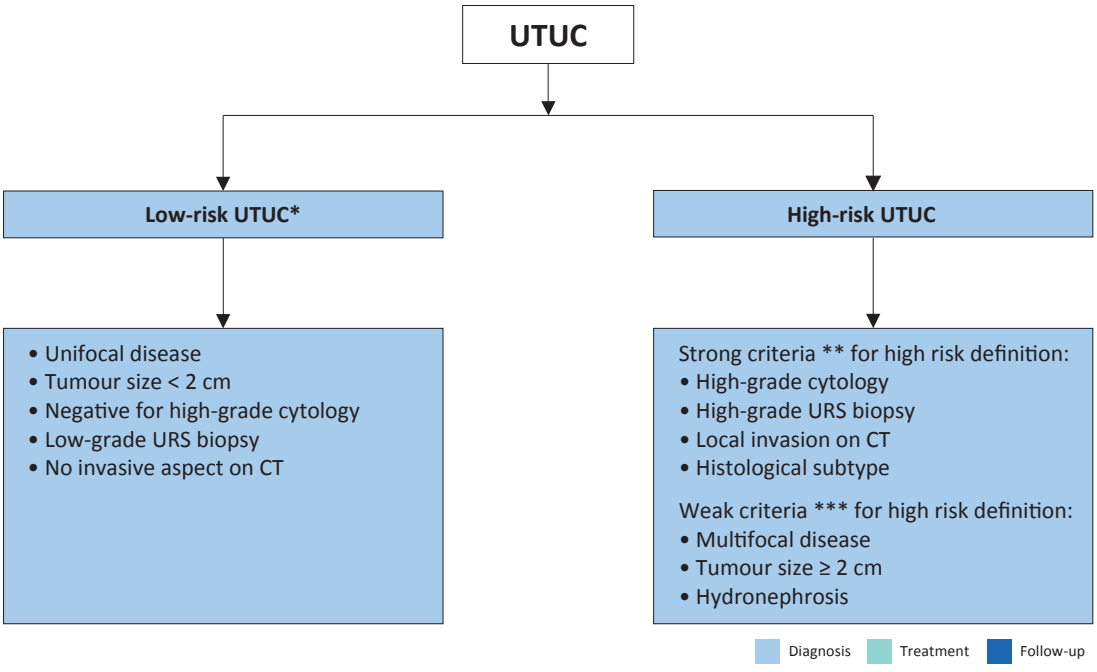
As tumour stage is difficult to assess clinically in UTUC, it is useful to stratify patients according to the low- and high risk of progression in order to identify those who are likely to benefit from kidney-sparing treatment and those who should be treated by radical nephroureterectomy [188, 189]. The factors to consider for the risk stratification are presented in Figure 6.1.

The level of evidence to consider individually size, multifocality and hydronephrosis as a surrogate for high-risk of progression remains low. Therefore, in the presence of low-grade disease associated with these factors, a shared decision-making process with the patient is important to discuss the therapeutic strategy (kidney-sparing strategy or RNU).

Pre-RNU models aiming at predicting which patient has > pT2 /non-organ-confined disease have been published [190-194]. Several risk stratification models have been assessed with the main aim to identify better patients eligible for kidney-sparing surgery [188, 189, 195-197].

Prognostic nomograms based on pre-operative factors and post-operative pathological characteristics are also available [169, 192, 198-203] and may be used when counselling patients regarding follow-up and administration of peri-operative chemotherapy. Nevertheless, despite a moderate to good discrimination accuracy, severe heterogeneity discourages its use in systematic ways.

Figure 6.1: Risk stratification of non-metastatic UTUC according to the risk of progression to a> pT2 /non-organ-confined disease



CT = computed tomography; URS = ureteroscopy; UTUC = upper urinary tract urothelial carcinoma.
** All these factors need to be present.*
***Any of these factors need to be present.*
****In the presence of low-grade tumour these factors are not strong predictors of invasive disease.*

6.3 Bladder recurrence

A meta-analysis of available data has identified significant predictors of bladder recurrence after RNU [22]. Three categories of predictors for increased risk of bladder recurrence were identified:

1. Patient-specific factors such as male gender, previous BC, smoking and pre-operative chronic kidney disease.
2. Tumour-specific factors such as positive pre-operative urinary cytology, tumour grade, ureteral location, multifocality, tumour diameter, invasive pT stage, and necrosis [204, 205].
3. Treatment-specific factors such as laparoscopic approach, extravesical bladder cuff removal, and positive surgical margins [22].

In addition, the use of diagnostic URS has been associated with a higher risk of developing bladder recurrence after RNU [206, 207]. Based on low-level evidence only, a single dose of intravesical chemotherapy after diagnostic/therapeutic ureteroscopy of non-metastatic UTUC has been suggested to lower the rate of intravesical recurrence, similarly to that after RNU [22].

6.4 Summary of evidence and recommendation for the prognosis of UTUC

Summary of evidence	LE
Important prognostic factors for risk stratification include tumour size, stage, grade, multifocality, hydronephrosis and different histological subtypes.	3
Models are available to predict pT2/non-organ confined disease and prognosis after RNU.	3
Patient, tumour, and treatment-related factors impact risk of bladder recurrence after both kidney-sparing management and RNU.	3
Currently, no molecular biomarkers are validated for clinical use.	3

Recommendation	Strength rating
Use prognostic factors to risk-stratify patients for therapeutic guidance.	Strong

7. DISEASE MANAGEMENT

All patients with suspicion of UTUC on imaging should be discussed in a multidisciplinary team prior to the initiation of treatment.

7.1 Localised low-risk disease

7.1.1 General considerations on kidney-sparing surgery

Kidney-sparing surgery for low-risk UTUC reduces the morbidity associated with radical nephroureterectomy (e.g., loss of kidney function), without compromising oncological outcomes [208]. In low-risk cancers, it is the preferred approach as survival is similar to that after RNU [208]. This option should therefore be discussed in all low-risk cases, irrespective of the status of the contralateral kidney, in a shared-decision making process with the patient. Recommendations for kidney-sparing management of UTUC are listed in Section 7.1.7.

7.1.2 Ureteroscopy

Endoscopic ablation should be considered in patients with clinically low-risk cancer [209, 210]. A flexible ureteroscope is useful in the management of pelvicalyceal tumours [211]. The patient should be informed of the need and be willing and able to comply with an early second-look URS [212] and stringent surveillance; complete tumour resection or destruction is necessary [212]. Nevertheless, a risk of disease progression remains with endoscopic management due to the suboptimal performance of imaging and biopsy for risk stratification and tumour biology [213]. A systematic review reported comparable survival outcomes after endoscopic treatment to radical nephroureterectomy at the cost of higher local recurrence rates and repeated interventions, but also with some uncertainties about long-term renal preservation after endoscopic treatment [214].

*7.1.3 **Percutaneous access***

Percutaneous management can be considered for low-risk UTUC in the renal pelvis [209, 215]. This may also be offered for low-risk tumours in the lower caliceal system that are inaccessible or difficult to manage by flexible URS. However, this approach is being used less due to the availability of improved endoscopic tools such as distal-tip deflection of recent ureteroscopes [210, 215]. Moreover, a risk of tumour seeding remains with percutaneous access [215].

*7.1.4 **Ureteral resection***

Segmental ureteral resection with adequate margins provides sufficient pathological specimens for staging and grading while preserving the ipsilateral kidney. Segmental resection of the proximal two-thirds of ureter is associated with higher failure rates than for the distal ureter [216, 217].

Distal ureterectomy with ureteroneocystostomy is indicated for low-risk tumours in the distal ureter that cannot be completely removed endoscopically [199, 216, 218]. A total ureterectomy with an ileal-ureteral substitution or renal autotransplantation with pyelocystostomy is technically feasible, but only in selected cases when a renal-sparing procedure is mandatory and the tumour is low risk [219, 220].

*7.1.5 **Chemo-ablation***

A single-arm phase III trial including 71 patients with biopsy-proven low-grade UTUC less than 15 mm showed that the use of mitomycin-containing reverse thermal gel (UGN-101) instillations (6 weekly induction) in a chemoablation setting via retrograde catheter to the renal pelvis and calyces was associated with a complete response rate in a total of 41 patients (58%) [221]. The most frequently reported all-cause adverse events (AEs) were: ureteric stenosis in 31 (44%), urinary tract infection in 23 (32%), haematuria in 22 (31%), flank pain in 21 (30%), nausea in 17 (24%) and 19/31 (61%) reported ureteric stenosis requiring treatment. Among the 41 patients with complete response, 29 received at least one maintenance instillation (median of 6), 23/41 (56%) remained disease free at one year [221].

*7.1.6 **Adjuvant instillations***

7.1.6.1 Upper urinary tract

The antegrade instillation of BCG or mitomycin C in the upper urinary tract via percutaneous nephrostomy after complete tumour eradication has been studied for CIS after kidney-sparing management [186, 222]. Retrograde instillation through a single-J open-ended ureteric stent is also used. Before both the antegrade and retrograde approach a nephro-ureterogram needs to rule out ureteric obstruction or leakage, asses that there is no infection and ensure a low pressure system to avoid pyelovenous influx during instillation/perfusion. The reflux obtained from a double-J stent has been used but this approach is suboptimal because the drug often does not reach the renal pelvis [223-226].

A systematic review and meta-analysis assessing the oncologic outcomes of patients with papillary UTUC or CIS of the upper tract treated with kidney-sparing surgery and adjuvant endocavitary treatment analysed the effect of adjuvant therapies (i.e., chemotherapeutic agents and/or immunotherapy with BCG) after kidney-sparing surgery for papillary non-invasive (Ta–T1) UTUCs and BCG for the treatment of upper tract CIS, finding no difference between the method of drug administration (antegrade vs. retrograde vs. combined approach) in terms of recurrence, progression, CSS, and OS; however, all included studies were underpowered and highly heterogeneous. Furthermore, the recurrence rates following adjuvant instillations are comparable to those reported in the literature in untreated patients, questioning their efficacy [227]. The analyses were based on retrospective small studies suffering from publication and reporting bias.

Recent evidence suggests that early single adjuvant intracavitary upper tract instillation of mitomycin C in patients with low-grade UTUC might reduce the risk of local recurrence [228]. The authors report limited complications related to the instillations but propose a retrograde pyelography before instillations are commenced to exclude contrast extravasation. This concept will need further evaluation in a randomised context [228].

7.1.6.2 Bladder

There are currently no data to support the use of bladder instillation of chemotherapy after kidney-sparing surgery as available RCTs included only patients who received RNU.

*7.1.7 **Recommendation for kidney-sparing management of localised low-risk UTUC***

Recommendation	Strength rating
Offer kidney-sparing management as primary treatment option to patients with low-risk tumours.	Strong

7.2 Localised high-risk disease

*7.2.1 **Radical nephroureterectomy***

7.2.1.1 Surgical approach

7.2.1.1.1 Open radical nephroureterectomy

Open RNU with bladder cuff excision is the standard treatment of high-risk UTUC, regardless of tumour location [13]. Radical nephroureterectomy must be performed according to oncological principles preventing tumour seeding [13]. Section 7.2.5 lists the recommendations for RNU.

7.2.1.1.2 Minimal invasive radical nephroureterectomy

Retroperitoneal metastatic dissemination and metastasis along the trocar pathway following manipulation of large tumours in a pneumoperitoneal environment may occur [229, 230]. Several precautions may lower the risk of tumour spillage:

1. avoid entering the urinary tract, except when performing a bladder cuff excision and only after prior clipping of the ureter and complete drainage of the bladder;
2. avoid direct contact between instruments and the tumour;
3. perform the procedure in a closed system. Avoid morcellation of the tumour and use an endobag for tumour extraction;
4. the kidney and ureter must be removed *en bloc* with the bladder cuff;
5. in invasive or large (T3/T4 and/or N+/M+) tumours an open approach is favoured, as the oncological outcomes may be better compared to minimally-invasive RNU [231, 232].

Laparoscopic RNU is safe in experienced hands when adhering to strict oncological principles. There is a tendency towards equivalent oncological outcomes after laparoscopic vs. open RNU [230, 233-236]. One prospective randomised study has shown that laparoscopic RNU is inferior to open RNU for non-organ- confined UTUC. However, this was a small trial (n = 80) [232]. Oncological outcomes after RNU have not changed significantly over the past three decades despite staging and surgical refinements [237]. In a population-based data set, a hospital volume of > 6 patients per year treated with RNU showed improvement of short-term outcomes (30- and 90-day mortality) and overall long-term survival [238]. A robot-assisted laparoscopic approach can be considered allowing comparable peri operative benefit as standard laparoscopic surgery [239-241], with data suggesting oncologic equivalence with the other approaches [242-244]; however, the risk of intravesical recurrence may be increased with both laparoscopic and robotic RNU compared to the open approach [245].

7.2.1.1.3 Bladder cuff management

Resection of the distal ureter and its orifice is performed because there is a considerable risk of tumour recurrence in this area and in the bladder [22, 216, 246-248]. Several techniques have been considered to simplify distal ureter resection, including the pluck technique, stripping, transurethral resection of the intramural ureter, and intussusception. None of these techniques has convincingly been shown to be equal to complete bladder cuff excision [23, 246].

7.2.1.1.4 Lymph node dissection

The use of a LND template is likely to have a greater impact on patient survival than the number of removed LNs [249]. Template-based and completeness of LND improves CSS in patients with muscle-invasive disease and reduces the risk of local recurrence [250]. Even in clinically [251] and pathologically [252] node-negative patients, LND improves survival. The risk of LN metastasis increases with advancing tumour stage [170]. Lymph node dissection appears to be unnecessary in cases of TaT1 UTUC because of the low risk of LN metastasis [253-256], however, tumour staging is inaccurate pre-operatively; therefore a template-based LND should be offered to all patients who are scheduled for RNU for high-risk UTUC. The templates for LND have been described [250, 257, 258].

*7.2.2 **Distal ureterectomy***

Distal ureterectomy for high-risk UTUC in the distal ureter only seems to be associated with similar oncological outcomes as RNU [208, 259]. This procedure can be performed with concomitant LN dissection. However,

given the low level of evidence, this approach should only be currently used in highly selected cases where the benefits may be greater than the potential risks.

*7.2.3 **Kidney-sparing surgery for imperative indications***

Kidney-sparing surgery, including ureteroscopy or segmental ureterectomy, can be considered on a case-by- case basis for patients with high-risk UTUC with imperative indications such as solitary kidney, bilateral UTUC, severe chronic kidney disease or any other comorbidity compromising the use of RNU. However, there is a greater risk of progression after kidney-sparing surgery for high- vs. low-risk UTUC with a direct impact on survival [208].

*7.2.4 **Peri-operative chemotherapy***

7.2.4.1 Neoadjuvant treatments

7.2.4.1.1 Chemotherapy

The primary advantage of neoadjuvant chemotherapy (NAC) is the ability to give cisplatin-based regimens when patients still have maximal renal function. Several retrospective studies evaluating the role of NAC have shown evidence of pathological downstaging and complete response rates at RNU [180, 260-263] with a direct impact on OS [194]. Furthermore, NAC has been shown to result in lower disease recurrence- and mortality rates compared to RNU alone, without compromising the use of definitive surgical treatment with a potential OS benefit [262, 264-266].

No RCTs have been published yet but prospective data from phase II trials showed that NAC based on cisplatin combination therapy was associated with a 14 - 19% pathological complete response rate in high-grade and/or cT2-T4N0M0 UTUC [267, 268]. In addition, final pathological stage was < ypT1 in more than 60% of included patients with acceptable toxicity profile. In a systematic review and meta-analysis comprising more than 800 patients, NAC has shown a pathologic partial response of 43% and a downstaging in 33% of patients, resulting in an OS and CSS survival benefit compared with RNU alone [269]. However, it is important to note that the evidence in the meta-analysis is not conclusive, given the significant bias and heterogeneity of the available data and the lack of distinction between truly neoadjuvant and downstaging chemotherapy.

7.2.4.1.2 Immunotherapy

Only a small phase II study including 10 patients with high-risk UTUC evaluated the efficacy of pembrolizumab in the neoadjuvant setting [270]. However, no pathological response was observed and one treatment-related death was reported. Thus, there is currently no evidence to support the use of neoadjuvant immunotherapy for high-risk UTUC.

7.2.4.2 Adjuvant treatments

7.2.4.2.1 Bladder instillations

The rate of bladder recurrence after RNU for UTUC is 22–47% [189, 246]. Two prospective randomised trials [271, 272] and two meta-analyses [273, 274] have demonstrated that a single post-operative dose of intravesical chemotherapy (mitomycin C, pirarubicin) 2–10 days after surgery reduces the risk of bladder tumour recurrence within the first years post-RNU in patients without a history of BC. Prior to instillation, a cystogram can be considered in case of concerns about drug extravasation. All studies showed a very low risk of adverse events. Intravesical chemotherapy has also been safely given at the time of RNU prior to bladder cuff opening, removing the need for a post- operative cystogram, but with low level data for efficacy [275].

Based on current evidence it is unlikely that additional instillations beyond one peri-operative instillation of chemotherapy further substantially reduce the risk of intravesical recurrence [276]. Whilst there is no direct evidence supporting the use of intravesical chemotherapy instillation of chemotherapy after kidney-sparing surgery, single- dose chemotherapy might also be effective in that setting as well. Management is outlined in Figures 7.1 and 7.2. One low-level evidence study suggested that bladder irrigation might reduce the risk of bladder recurrence after RNU [277].

7.2.4.2.2 Systemic Chemotherapy

A phase III multicentre prospective RCT (n = 261) evaluating the benefit of four cycles of adjuvant gemcitabine-platinum combination chemotherapy initiated within 90 days after RNU vs. surveillance has reported a significant improvement in disease-free survival (DFS) in patients with pT2–pT4, N (any) or positive (pT any, N1–3) M0 UTUC (3 year DFS 71% vs 50%; 5 year DFS 63% vs 46%. HR 0.54 ; CI 0.36-0.79; 3 & 5 year MFS 19 % improvement HR 0.55 CI 0.0.36-0.77) [278]. Patients were stratified to gemcitabine/cisplatin or gemcitabine/carboplatin chemotherapy based on GFR alone with benefit seen irrespective of chemotherapy type. There was a non-significant trend towards improved OS (12% at 3 years) but as the study had met its primary endpoint of 3

year DFS, it closed early, leaving it underpowered for the secondary endpoint of OS. The main potential limitation of using adjuvant chemotherapy is the concern that renal function may deteriorate after RNU precluding cisplatin use in patients who could benefit from this [279, 280]. A review of peri-operative predictors of decline in renal function after RNU showed three month GFR levels of around 50 mls/min [281]. With split dose and hydration cisplatin may be considered in patients with a GFR down to 45 mL/min. Table 2 outlines the eligibility criteria for platinum chemotherapy.

In a retrospective study histological subtypes of UTUC exhibit different survival rates and adjuvant chemotherapy was only associated with an OS benefit in patients with pure UC [282]. However, whilst histological subtypes of UTUC exhibit different survival rates in retrospective studies, adjuvant chemotherapy should be considered where UC is the dominant pathology.

Table 2: Definitions of platinum-eligibility for systemic treatment of urothelial carcinoma. [2]

Platinum-eligible		**Platinum-ineligible**
Cisplatin-eligible	**Carboplatin*-eligible**	
ECOG PS 0-1 ***and*** GFR > 50–60 mL/min ***and*** Audiometric hearing loss grade < 2 ***and*** Peripheral neuropathy grade < 2 ***and*** Cardiac insufficiency NYHA class < III	ECOG PS 2 *or* GFR 30–60 mL/min ***or*** not fulfilling other cisplatin-eligibility criteria	Any of the following: • GFR < 30mL/min • ECOG PS > 2 • ECOG PS 2 *and* GFR < 60mL/min • Comorbidites > Grade 2

**** Carboplatin is not indicated for neoadjuvant treatment***

7.2.4.2.3 Immunotherapy

In a phase III, multicentre, double-blind RCT involving patients with high-risk muscle-invasive UC who had undergone radical surgery (pT3, pT4a, or pN+), adjuvant nivolumab improved DFS compared to placebo in the intention-to-treat population (20.8 vs. 10.8 months) and among patients with a programmed death-ligand 1 (PD-L1) expression level of 1% or more [283]. The patient population predominantly consisted of BC patients post-radical cystectomy, with an additional smaller cohort of patients with UTUC post-RNU. The median recurrence-free survival outside the urothelial tract in the entire intention-to-treat population was 22.9 months for nivolumab and 13.7 months for placebo. Treatment-related adverse events > grade 3 occurred in 17.9% of the nivolumab group and 7.2% of the placebo group. On subgroup analysis, patients with UTUC included in this study did not seem to benefit from adjuvant nivolumab, which requires further follow-up and analysis. Nonetheless, the European Medicines Agency (EMA) approved nivolumab as monotherapy for the adjuvant treatment of patients with muscle-invasive UC with tumour cell PD-L1 expression > 1%, who are at high risk of recurrence after radical surgery and who decline or are unfit for adjuvant chemotherapy [284].

A network meta-analysis suggests superior oncological benefit for adjuvant platinum-based chemotherapy over immune checkpoint inhibitors in patients treated with radical surgery for UTUC [285].

7.2.4.2.4 Radiotherapy

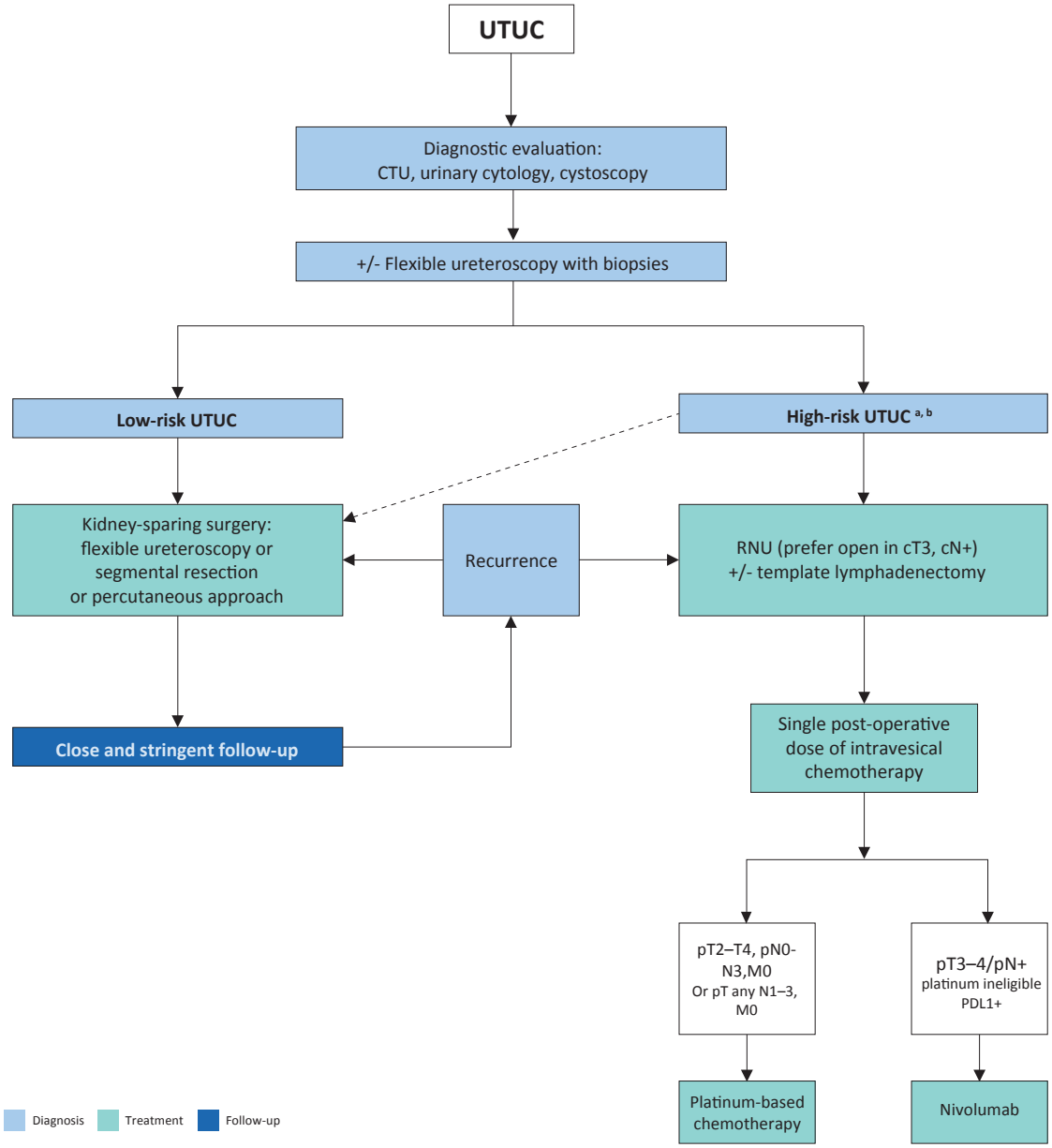
Adjuvant radiation therapy has been suggested to control loco-regional disease after surgical removal. The data remains controversial and insufficient for conclusions [286-289]. Moreover, its added value to chemotherapy remains questionable [288].

7.2.5 *Summary of evidence and recommendations for the management of high-risk non-metastatic UTUC*

Summary of evidence	LE
Radical nephroureterectomy is the standard treatment for high-risk UTUC, regardless of tumour location.	2a
Open, laparoscopic and robotic approaches have similar oncological outcomes for organ-confined UTUC.	2a
Failure to completely remove the bladder cuff increases the risk of BC recurrence.	3
Lymphadenectomy improves survival in muscle-invasive UTUC.	3
Post-operative platinum-based adjuvant chemotherapy improves disease-free survival.	1b
Single post-operative intravesical instillation of chemotherapy lowers the BC recurrence rate.	1b

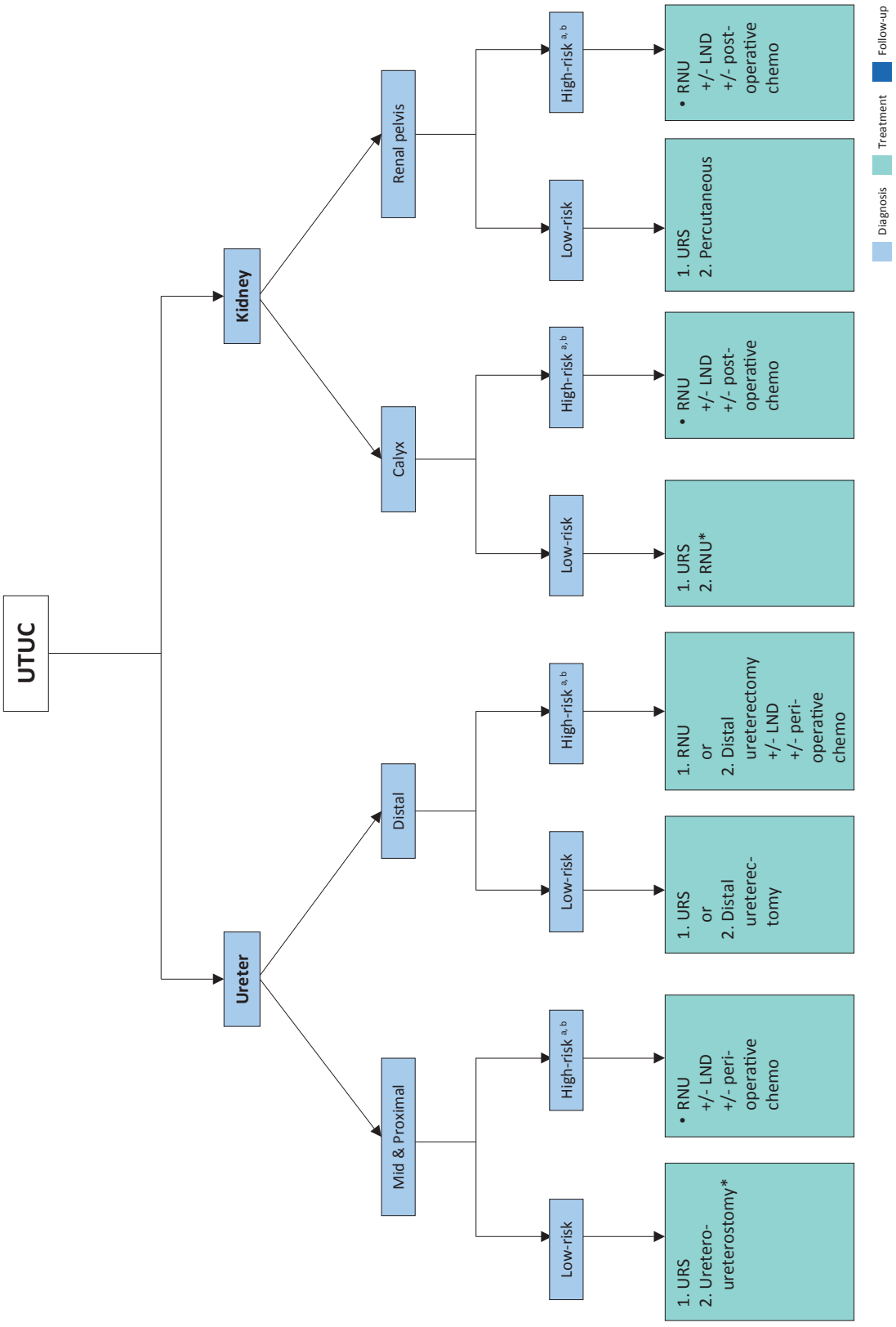
Recommendations	Strength rating
Perform radical nephroureterectomy (RNU) in patients with high-risk non-metastatic upper tract urothelial carcinoma (UTUC).	Strong
Perform open RNU in non-organ confined UTUC.	Weak
Perform a template-based lymphadenectomy in patients with high-risk non-metastatic UTUC.	Weak
Offer adjuvant platinum-based chemotherapy after RNU to eligible patients with pT2–T4 and/or pN+ disease.	Strong
Deliver a post-operative bladder instillation of chemotherapy to lower the intravesical recurrence rate in patients without a history of BC.	Strong
Discuss adjuvant nivolumab with patients unfit for, or who declined, platinum-based adjuvant chemotherapy for > pT3 and/or pN+ disease after previous RNU alone or > ypT2 and/or ypN+ disease after previous neoadjuvant chemotherapy, followed by RNU.	Weak
Offer distal ureterectomy to selected patients with high-risk tumours limited to the distal ureter.	Weak
Discuss kidney-sparing management to high-risk patients with imperative indication on a case- by-case basis, in a shared-decision making process with the patient despite the higher risk of disease progression.	Strong

Figure 7.1: Proposed flowchart for the management of UTUC



a: In patients with solitary kidney consider a more conservative approach.
b: In low-grade patients without invasive features consider a more conservative approach.
CTU = computed tomography urography; RNU = radical nephroureterectomy; UTUC = upper urinary tract urothelial carcinoma.

Figure 7.2: Surgical treatment according to location and risk status



a: In patients with solitary kidney consider a more conservative approach.
b: In low-grade patients without invasive features consider a more conservative approach.
1 = first treatment option; 2 = secondary treatment option.
**In case not amendable to endoscopic management.*
LND = lymph node dissection; RNU = radical nephroureterectomy; URS = ureteroscopy; UTUC = upper urinary tract urothelial carcinoma.

7.3 Metastatic disease

*7.3.1 **Clinical loco-regional lymph node metastases***

Evidence is lacking regarding the optimal management of clinical node-positive disease. Patients with clinically N+ UTUC should be offered downstaging first-line platinum-based chemotherapy. In patients whose cancer responds or who have stable disease, maintenance avelumab can be offered, especially in cN2 disease [290]. Depending on the extent of the nodal disease (i.e., cN1/N2) surgical resection with LN dissection can be discussed in a multidisciplinary team and with the patient when responding on after initial systemic therapy. In patients whose cancer progress, second-line treatment can be offered, similar to metastatic disease [291, 292].

*7.3.2 **Distant metastases***

7.3.2.1 Systemic treatments - First-line setting

7.3.2.1.1 Enfortumab vedotin + pembrolizumab combination therapy

For more than 23 years despite multiple attempts with new agents and/or combinations of treatments, platinum-based chemotherapy remained standard of care for previously untreated advanced or metastatic urothelial cancer. In October 2023, the landscape changed dramatically with the EV302 phase III randomised multi-centre study. This compared the combination of the nectin 4 directed antibody-drug conjugate enfortumab vedotin with the check point inhibitor pembrolizumab, (EV+P) with platinum based combination chemotherapy (gemcitabine-cisplatin or gemcitabine -carboplatin. See table 2 for definition of cisplatin eligibility).

This study showed significant improvement in both PFS (HR 0.45 (0.38-0.54) and OS (HR 0.47 (0.38-0.58) with RR of 68% (versus 44%) and CR 29% . OS benefit was seen across sub groups regardless of cisplatin eligibility. The most common grade 3 or above TRAE of special interest included skin reactions (15.5%) , peripheral neuropathy (6.8%) and hyperglycaemia (6.1%). The proportion of UTUC patients in this study is not yet known.

Sequencing of treatment after Ev+Pembro is currently unclear and later line treatments will depend upon what agents the patient has previously received (Figure 7.3).

7.3.2.1.2 Patients ineligible for EV+Pembro and fit for cisplatin-based combination chemotherapy

Upper tract UC and urothelial BC both respond to systemic platinum-based chemotherapy. Eligibility to platinum-based chemotherapy in the metastatic setting is based on the same criteria outlined in Table 2. A retrospective analysis of three RCTs showed that primary tumour location in the lower- or upper urinary tract had no impact on progression-free survival (PFS) or OS in patients with locally-advanced or metastatic UC treated with platinum-based combination chemotherapy [293]. Therefore, cisplatin-containing combination chemotherapy is the standard treatment for advanced or metastatic UTUC ineligible for EV + Pembro [2]. A number of cisplatin-containing chemotherapy regimens have proven efficacy although gemcitabine and cisplatin are the most widely used. The use of cisplatin-based chemotherapy is widely considered in patients with eGFR > 45 mL/min [293].

The efficacy of immunotherapy using PD1 or PD-L1 inhibitors has been evaluated in the first-line setting for the treatment of cisplatin/carboplatin-fit patients with metastatic UC, including those with UTUC [294]. First-line immune checkpoint inhibitors or the combination of platinum-based chemotherapy with immune checkpoint inhibitors have not previously resulted in positive significant survival advantages were thus not previously recommended [295-297]. These studies included both cisplatin and carboplatin combinations.

A phase III RCT in advanced/metastatic urothelial cancer has now shown an overall benefit from the addition of nivolumab to chemotherapy (gemcitabine-cisplatin). Median OS was improved (21.7 months v 18.9 months HR 0.78 (0.63-0.96) as well as median PFS (7.9 months versus 7.6 months HR 0.72 (0.59-0.88). Objective RR were 57.6% compared with 43.1 % for chemotherapy alone [298]. Although there is no sub-group analysis based on tumour position in this study, 12.6% of patients had UTUC.

7.3.2.1.3 Patients ineligible for Ev+Pembro and unfit for cisplatin-based combination chemotherapy

Carboplatin-based chemotherapy is recommended in patients unfit for cisplatin [2]. Carboplatin with gemcitabine is the preferred regimen [299], irrespective of PDL-1 status. In a recent critical re-analysis of RCTs comparing OS after cisplatin vs. carboplatin-based regimens in advanced UC, cisplatin conferred a minor OS benefit compared to carboplatin [300].

7.3.2.1.4 Maintenance therapy after first-line platinum-based chemotherapy

Maintenance avelumab is recommended in patients with complete/partial response or stable disease after 4–6 cycles of platinum-based chemotherapy, given in the first line setting only. Data from a phase III RCT showed that the use of avelumab maintenance therapy after 4 to 6 cycles of gemcitabine plus cisplatin or carboplatin (started within 10 weeks of completion of first-line platinum-based chemotherapy) significantly prolonged

OS as compared to best supportive care alone in those patients with advanced or metastatic UC who did not experience disease progression during, or responded to, first-line chemotherapy (HR: 0.69; 95% CI: 0.56–0.86) [290, 301]. An increase in median OS from 14 to 21 months was observed with avelumab. Although no subgroup analysis based on tumour location was available in this study, almost 30% of the included patients had UTUC. Similarly, in a phase II study comprising 108 patients with metastatic UC achieving at least stable disease on first-line platinum-based chemotherapy, maintenance pembrolizumab improved PFS compared to placebo (5.4 vs. 3.0 months) [302].

7.3.2.1.5 Patients unfit for any combination therapy

Pembrolizumab or atezolizumab are alternative choices for patients who are PD-L1 positive and not eligible/fit for platinum-based chemotherapy. In a single-arm phase II trial (n = 370) of cisplatin-ineligible UC, pembrolizumab monotherapy was associated with an objective response rate of 26% in 69 metastatic UTUC patients [303]. In the overall cohort, a PD-L1 expression of 10% was associated with a greater response rate to pembrolizumab. Treatment-related toxicity was in line with previous studies. In a single-arm phase II trial (n = 119) of cisplatin-ineligible UC, atezolizumab monotherapy was associated with an objective response rate of 39% in 33 (28%) metastatic UTUC patients [304]. Median OS in the overall cohort was 15.9 months and treatment-related toxicity was in line with previous studies [296].

7.3.2.2 Systemic treatments - later line setting

Subsequent treatments depend on the type of treatment given in the first line setting.

7.3.2.2.1 Platinum based chemotherapy

Platinum based chemotherapy should be the second line treatment of choice if not received in the first line setting. No data supports the use of maintenance avelumab outside of the first line setting.

7.3.2.2.2 Immunotherapy

A phase III RCT including 542 patients who received prior platinum-based chemotherapy for advanced UC showed that pembrolizumab decreased the risk of death compared to second-line chemotherapy (the investigator's choice of paclitaxel, docetaxel, or vinflunine); median OS: 10.3 months for pembrolizumab and 7.4 months for chemotherapy (HR: 0.73; 95% CI: 0.59–0.91) [305]. Responses were more frequent and durable for pembrolizumab compared to chemotherapy (21% vs. 11%). In the UTUC subgroup (n = 75/13.8%), the OS benefit seemed larger (50%).

The IMVigor211 trial explored atezolizumab in PD-L1-positive tumours in patients with tumours which relapsed after platinum-based chemotherapy; it failed to show a significant OS advantage of atezolizumab compared to second-line chemotherapy [306].

Other immunotherapies such as nivolumab [307], avelumab [308, 309] and durvalumab [310] have shown objective response rates ranging from 17.8% [310] to 19.6% [307] and median OS ranging from 7.7 months to 18.2 months in patients with platinum-resistant metastatic UC. These results were obtained from single-arm phase I or II trials only and the number of UTUC patients included in these studies was only specified for avelumab (n = 7/15.9%) without any subgroup analysis based on primary tumour location [309].

The immunotherapy combination of nivolumab plus ipilimumab has shown significant anti-tumour activity with objective response rate up to 38% in a phase I/II multicentre trial including 78 patients with metastatic UC experiencing disease progression after platinum-based chemotherapy [311]. Although UTUC patients were included in this trial, no subgroup analysis was available. Other immunotherapy combinations may be effective in the second-line setting but data are currently limited [312].

7.3.2.2.3 Novel agents

Fibroblast growth factor receptors (FGFR) inhibition

Erdafitinib, a pan-FGFR tyrosine kinase inhibitor of FGFR1–4, was associated with a 40% radiological response rate according to the Response Evaluation Criteria in Solid Tumours (RECIST) in a phase II trial of 99 patients with locally-advanced or metastatic UC who progressed after first-line chemotherapy and harboured a FGFR DNA genomic alterations (FGFR2/3 fusions or FGFR3 mutations) [313]. This study included 23 UTUC patients with visceral metastases showing a 43% radiological response rate. The subsequent phase III Thor trial randomised 266 patients with advanced UC who had had similar mutations and had experienced disease progression after 1-2 lines of previous treatment, to treatment with either erdafitinib or investigators choice of chemotherapy (vinfunine or docetaxel). Significant improvements in median OS, (4.3 months; HR 0.64;CI 0.47-0.88), PFS 2.9 months (58; CI 0.44-0.78) and a 36% risk reduction in death were observed. 33.5 % of patient in this study had UTUC [314]. As the rate of activating alterations of FGFR3 is higher in UTUC than in bladder cancer [315] a potentially greater impact

of FGR3 targeting agents is anticipated. UTUC patients should be tested for FGFR alterations (FGFR2/3 mutations or FGFR3 fusions) prior to erdafitinib treatment.

Antibody drug conjugates (ADC)

A phase II study enrolled 89 patients (of whom 43% had UTUC) with cisplatin-unfit metastatic UC experiencing disease progression after therapy with PD-1 or PD-L1 inhibitors. All patients received the antibody–drug conjugate enfortumab vedotin. The objective radiological response rate (RECIST) was 52% of which 20% of patients achieved complete response [316]. In a phase III trial of enfortumab vedotin for the treatment of patients with locally- advanced or metastatic UC who had previously received platinum-containing chemotherapy and had disease progression during or after treatment with a PD-1 or PD-L1 inhibitor, enfortumab vedotin significantly prolonged survival as compared to standard chemotherapy (median OS 12.88 vs. 8.97 months) [317].

In an open-label phase II trial a total of 108 patients with metastatic UC who progressed after platinum- based chemotherapy and checkpoint inhibitors were treated with the antibody-drug conjugate sacituzumab govitecan. The objective radiological response rate was 27%, with median duration of response of 7.2 months, median PFS of 5.4 months and median OS of 10.9 months. However, the proportion of patients with UTUC was not mentioned in the publication [318].

A pre-planned subgroup analysis from the phase III RANGE trial assessed the impact on outcomes and safety of ramucirumab added to docetaxel after disease progression on both platinum-based chemotherapy and immune checkpoint inhibitors [319]. Median PFS was 3.15 months on ramucirumab/docetaxel vs. 2.73 months on placebo/docetaxel (HR: 0.786; 95% CI: 0.404–1.528, p = 0.4877). This trend for ramucirumab benefit occurred despite the ramucirumab arm having a higher percentage of patients with poorer prognosis. However, these findings need confirmation by further studies, as this analysis is limited by patient numbers and an imbalance in the treatment arms.

7.3.2.3 Surgery

7.3.2.3.1 Radical nephroureterectomy

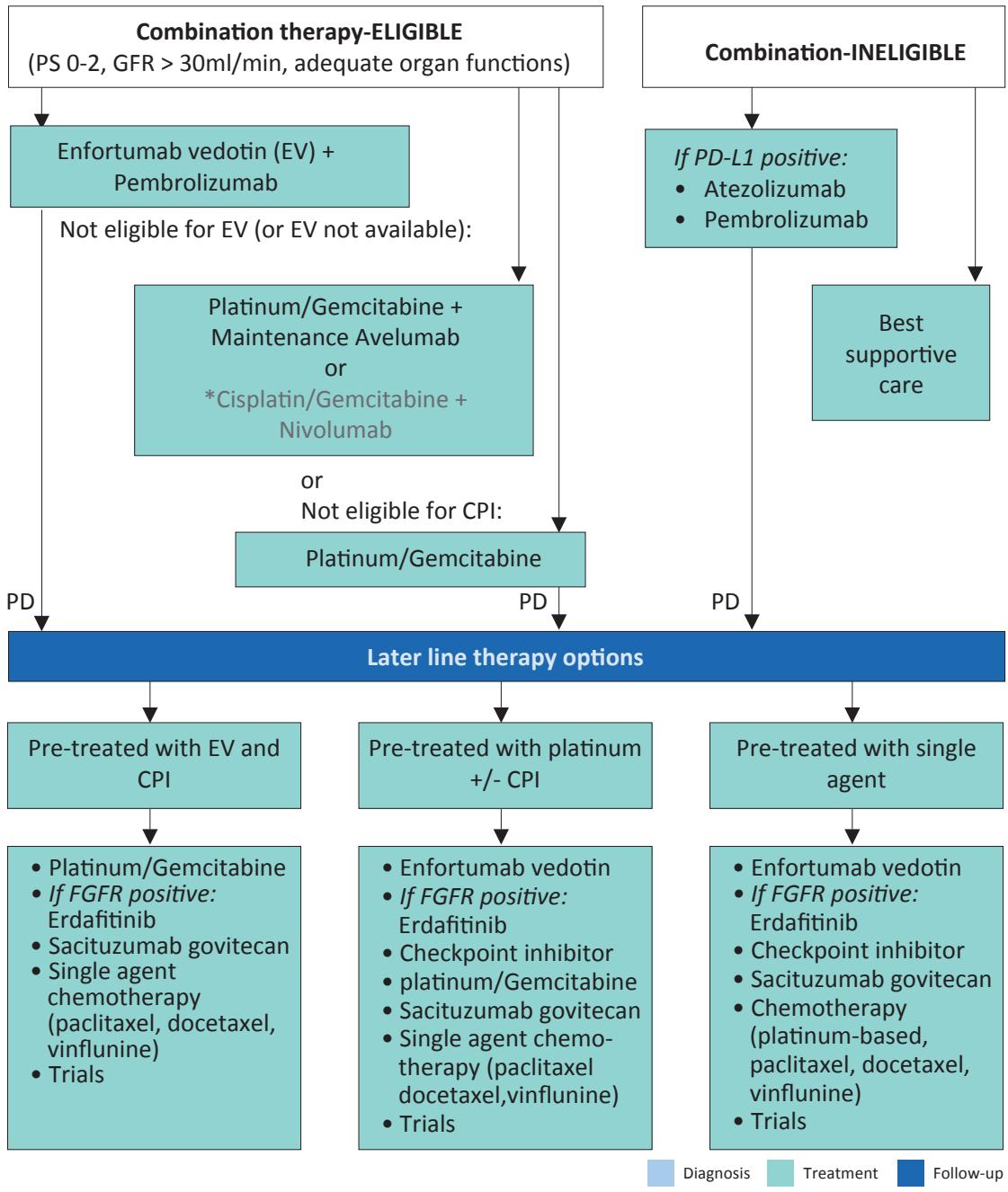
Data regarding RNU in the metastatic setting are lacking with mainly retrospective observational studies [320-322].

Although evidence remains very limited, RNU may be associated with CSS [321, 323, 324] and OS benefit in selected patients, especially those fit enough to receive cisplatin-based chemotherapy [320, 321]. It is noteworthy that these benefits may be limited to those patients with only one metastatic site [321]. Nonetheless, given the high risk of bias of the observational studies addressing RNU for metastatic UTUC, indications for RNU in this setting should mainly be reserved for palliative patients, aimed at controlling symptomatic disease [26, 124].

7.3.2.3.2 Metastasectomy

There is no UTUC-specific study supporting the role of metastasectomy in patients with advanced disease. Reports suggesting that resection of metastatic lesions could be safe and oncologically beneficial in selected patients should be interpreted with caution [325-329]. In the absence of data from RCTs, patients should be evaluated on an individual basis and the decision to perform a metastasectomy (surgically) should be made following a shared decision-making process with the patient.

Figure 7.3 Flowchart for the management of metastatic upper tract urothelial carcinoma



**In view of lack of subgroup analysis data for UTUC*
EV = enfortumab vedotin; FGFR = fibroblast growth factor receptor; GFR = glomerular filtration rate; PS = performance status; CPI=checkpoint inhibitor; PD-L1= programmed death-ligand 1; PD= programmed death

7.3.3 Summary of evidence and recommendations for the treatment of metastatic UTUC

Summary of evidence	LE
Enfortmab vedotin + Pembrolizumab offers an overall survival benefit compared to gemcitabine-cisplatin in the 1st line setting.	1b
Cisplatin-based combination chemotherapy can improve median survival.	2
Cisplatin-containing combination chemotherapy is the standard of care in advanced or metastatic patients fit enough to tolerate cisplatin and who are ineligible for Enfortumab + Pembrolizumab.	1b
Cisplatin-containing combination chemotherapy in combination with nivolumab offers a survival advantage compared with chemotherapy alone in the 1st line setting.	1b

Carboplatin-based combination chemotherapy offers a survival benefit in cisplatin unfit patients.	1b
Non-platinum combination chemotherapy has not been tested against standard chemotherapy in patients who are fit or unfit for cisplatin combination chemotherapy.	4
Maintenance avelumab is associated with an OS advantage compared with best supportive care in patients who did not have disease progression after 4 to 6 cycles of gemcitabine plus either cisplatin or carboplatin.	1b
PD-1 inhibitor pembrolizumab has been approved for patients who have experienced disease progression during or after previous platinum-based chemotherapy and did not receive previous immune therapy based on the results of a phase III trial.	1b
PD-1 inhibitor nivolumab has been approved for patients that have experienced disease progression during or after previous platinum-based chemotherapy and did not receive previous immune therapy based on the results of a phase II trial.	2a
PD-1 inhibitor pembrolizumab has been approved for patients with advanced or metastatic UC unfit for platinum-based first-line chemotherapy based on the results of a phase II trial but use of pembrolizumab is restricted to PD-L1 positive patients.	2a
PD-L1 inhibitor atezolizumab has been approved for patients with advanced or metastatic UC unfit for platinum-based first-line chemotherapy based on the results of a phase II trial, but use of atezolizumab is restricted to PD-L1 positive patients.	2a
Erdafitinib was associated with improved overall survival in platinum-refractory patients with locally-advanced or metastatic UC and FGFR DNA genomic alterations (FGFR2/3 mutations or FGFR3 fusions).	1b
Enfortumab vedotin was associated with OS benefit in patients who had previously received platinum-containing chemotherapy and experienced disease progression during or after treatment with a PD-1 or PD-L1 inhibitor.	1b
Palliative nephroureterectomy can improve quality of life by controlling symptomatic disease.	3
RNU can confer a survival benefit in highly selected patients with metastatic UC e.g., after response to platinum-based combination chemotherapy with limited metastatic burden.	4

Recommendations	**Strength rating**
Offer Enfortumab vedotin in combination with pembrolizumab as first line treatment to patients with advanced/metastatic disease.	Strong
First-line treatment for platinum-eligible patients who are unsuitable/ineligible for Enfortumab + Pembrolizumab	
Offer platinum combination chemotherapy to platinum-eligible patients.	Strong
Offer cisplatin based chemotherapy with gemcitabine-cisplatin + nivolumab in cisplatin eligible patients.	Weak
Offer cisplatin-based chemotherapy with gemcitabine/cisplatin or HD-MVAC to cisplatin-eligible patients.	Strong
Offer gemcitabine/carboplatin chemotherapy to cisplatin-ineligible patients.	Strong
Offer maintenance avelumab to patients who did not have disease progression after 4 to 6 cycles of platinum-based combination chemotherapy.	Strong
First-line treatment in patients ineligible for any combination therapy	
Offer checkpoint inhibitors pembrolizumab or atezolizumab to patients with PD-L1 positive tumours.	Weak
Later lines of treatment	
Offer platinum based combination chemotherapy as second line treatment of choice if not received in the first line setting.	Strong
Offer checkpoint inhibitor (pembrolizumab) to patients with disease progression during or after platinum-based combination chemotherapy for metastatic disease who did not receive maintenance avelumab.	Strong
Offer enfortumab vedotin to patients previously treated with platinum-containing chemotherapy and who had disease progression during or after treatment with a PD-1 or PD-L1 inhibitor.	Strong

Test UTUC patients for FGFR alterations (FGFR2/3 mutations or FGFR3 fusions) prior to erdafitinib treatment.	Strong
Offer erdafitinib as an alternative subsequent-line therapy to patients: • previously treated with platinum-containing chemotherapy; • who had disease progression during or after treatment with a PD-1 or PD-L1 inhibitor; • who harbour FGFR DNA genomic alterations (FGFR2/3 mutations or FGFR3 fusions).	Strong
Only offer vinflunine to patients with metastatic disease as second-line treatment if immunotherapy or combination chemotherapy is not feasible. Alternatively, offer vinflunine as third- or subsequent-line treatment.	Strong
Offer nephroureterectomy as a palliative treatment to symptomatic patients with resectable locally-advanced tumours.	Weak

DNA = deoxyribonucleic acid; FGFR = fibroblast growth factor receptors; HD-MVAC = high-dose intensity methotrexate, vinblastine, adriamycin plus cisplatin; PD-L1 = programmed death ligand 1.

8. FOLLOW-UP

The aims for follow-up after treatment for UTUC are to comply with patient rehabilitation needs, to detect recurrent or new primary tumours within the urothelium, and to detect regional and distant metastases. Bladder recurrence is not considered a distant recurrence. Unfortunately, the heterogeneity of available studies on disease-recurrence in UTUC is significant, and recommendations on follow-up have a low level of evidence at best.

After previous RNU for low-risk tumours bladder follow-up should adopt the NMIBC follow-up protocol for low-risk disease , a cystoscopy at three months post-operatively, a subsequent cystoscopy 9 months later and yearly cystoscopies for 5 years [330]. Screening for metastases during follow-up is not mandatory. Due to the low risk of contralateral upper tract recurrence routine imaging should be discussed on an individual basis [331].

When RNU has been performed for high-risk tumours, stringent follow-up is mandatory to detect metachronous bladder tumours (probability increases over time [332]), local recurrence, and distant metastases. The risk of bladder recurrences and other-site recurrences decreases 4 years after RNU, suggesting that less vigorous annual cystoscopies and cross-sectional imaging including CT urographies thereafter may apply [333]. For high risk, please consult the recommendations.

After kidney-sparing management for low-risk UTUC, and where no subsequent upstaging or upgrading occurred after the early second-look ureteroscopy after 6-8 weeks [212] or was found in the resection specimen after segmental ureteric resection, cystoscopy and CT-urography should be carried out at 3 and 6 months, and then yearly for 5 years. The risk for bladder recurrences beyond 5 years is limited (6%) [334].

In patients treated with kidney-sparing for high-risk tumours, the indication (imperative vs. non-imperative) affects the surveillance regimen by the consequences of recurrent disease. Still, the ipsilateral UUT requires careful and long-term follow-up due to the high risk of disease recurrence [211, 335, 336] and progression following RNU, even beyond 5 years [337].

Surveillance regimens are based on CT urography, cystoscopy and urinary cytology [332, 338]. There are, however, several unanswered questions related to the optimal follow-up of patients treated for both low-risk and high-risk UTUC, of which some are:

- The added value of new urinary markers compared to cytology in voided urine samples [339].
- The effect of the Paris System on sensitivity and specificity of voided and selective urinary cytology during follow-up of UTUC, especially in high-risk tumours [340].
- If adjuvant upper tract instillations have been administered after endourologic kidney-sparing management, will that allow for less vigorous follow-up?
- The role of ureteroscopies of the ipsilateral upper urinary tract during follow-up after endourologic kidney-sparing treatment vs. CT urography and voided urinary cytology.

Additionally, it is not known how patients with Lynch syndrome, without and with UTUC, should be screened of followed long-term given the inadequacy of surveillance based on urinalysis for nonvisible haematuria [341] and urine cytology [342], particularly in those individuals who are MSH2 mutation carriers [53] and those who already have developed a UTUC. Section 8.1 presents the summary of evidence and recommendations for follow-up of UTUC.

8.1 Summary of evidence and recommendations for the follow-up of UTUC

Summary of evidence	LE
Follow up should be based on risk stratification and the type of treatment.	3

Recommendations	Strength rating
After radical nephroureterectomy	
Low-risk tumours	
Perform cystoscopy at three months. If negative, perform subsequent cystoscopy 9 months later and then yearly, for 5 years.	Weak
High-risk tumours	
Perform cystoscopy and urinary cytology at 3 months. If negative, repeat subsequent cystoscopy and cytology every 3 months for a period of 2 years, and every 6 months thereafter until 5 years, and then yearly.	Weak
Perform computed tomography (CT) urography and chest CT every 6 months for 2 years, and then yearly.	Weak
After kidney-sparing management	
Low-risk tumours	
Perform cystoscopy and CT urography at 3 and 6 months, and then yearly for 5 years.	Weak
Perform ureteroscopy (URS) at 3 months if no second-look ureteroscopy was performed.	Weak
High-risk tumours	
Perform second-look URS and cytology in 6 weeks. If no residual tumour follow similar follow-up principles as for high-risk disease treated with radical nephroureterectomy.	Weak

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10. CONFLICT OF INTEREST

All members of the Non-Muscle-Invasive Bladder Cancer Guidelines working panel have provided disclosure statements on all relationships that they have that might be perceived to be a potential source of a conflict of interest. This information is available on the European Association of Urology website: http://uroweb.org/guideline/upper-urinary-tract-urothelial-cell-carcinoma/.

This guidelines document was developed with the financial support of the European Association of Urology. No external sources of funding and support have been involved. The EAU is a non-profit organisation, and funding is limited to administrative assistance and travel and meeting expenses. No honoraria or other reimbursements have been provided.

11. CITATION INFORMATION

The format in which to cite the EAU Guidelines will vary depending on the style guide of the journal in which the citation appears. Accordingly, the number of authors or whether, for instance, to include the publisher, location, or an ISBN number may vary.

The compilation of the complete Guidelines should be referenced as:
EAU Guidelines. Edn. presented at the EAU Annual Congress Paris 2024. ISBN 978-94-92671-23-3.

If a publisher and/or location is required, include:
EAU Guidelines Office, Arnhem, The Netherlands: http://uroweb.org/guidelines/compilations-of-all-guidelines/

References to individual guidelines should be structured in the following way:
Contributors' names. Title of resource. Publication type. ISBN. Publisher and publisher location, year.

EAU - EANM - ESTRO - ESUR - ISUP - SIOG Guidelines on

Prostate Cancer

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European Association of Urology

EANM European Association of Nuclear Medicine — Biomedical Imaging and Therapy for Personalized Healthcare

SIOG International Society of Geriatric Oncology

European Society of Urogenital Radiology

ESTRO European Society for Radiotherapy & Oncology

EUROPA UOMO The Voice of Men with Prostate Cancer in Europe

International Society of Urological Pathology

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1. INTRODUCTION

1.1 Aims and scope

The Prostate Cancer (PCa) Guidelines Panel have prepared this guidelines document to assist medical professionals in the evidence-based management of PCa.

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

1.2 Panel composition

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

All imaging sections in the text have been developed jointly with the European Society of Urogenital Radiology (ESUR) and the European Association of Nuclear Medicine (EANM). Representatives of the ESUR and the EANM in the PCa Guidelines Panel are (in alphabetical order): Dr. A. Farolfi, Dr. D. Oprea-Lager, Prof.Dr. O. Rouvière and Dr. I.G. Schoots.

All radiotherapy (RT) sections have been developed jointly with the European Society for Radiotherapy & Oncology (ESTRO). Representatives of ESTRO in the PCa Guidelines Panel are (in alphabetical order): Prof.Dr. G. De Meerleer, Prof.Dr. A.M. Henry, and Prof.Dr. T. Wiegel.

The International Society of Urological Pathology is represented by Prof.Dr. A. van Leenders.

Dr. E. Briers, expert Patient Advocate Hasselt-Belgium representing the patient voice as delegated by the European Prostate Cancer Coalition/Europa UOMO.

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/prostate-cancer/.

1.3 Available publications

A quick reference document (Pocket guidelines) is available. This is an abridged version 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 2024 document presents an update of the 2023 EAU-EANM-ESTRO-ESUR-ISUP-SIOG PCa Guidelines publication.

1.4.2 Summary of changes

The literature for the complete document has been assessed and all chapters of the 2024 PCa Guidelines have been updated. New data have been included in the following sections, resulting in new sections, and new and revised recommendations:

- An update in section 4.4 regarding the 2016 Cambridge Prognostic Groups.
- Restructure of section 5 – Diagnostic Evaluation to separate biopsy indication, biopsy strategy and biopsy approach.
- Incorporation of new text and references throughout section 5 including a new subsection 5.3.4 on tissue samples for homologous recombination repair (HRR)-testing and 5.3.5.7 on Intra-operative assessment of surgical margin status. Update on Table 5.6, Table 5.7, Figure 5.2 and a new section in section 5.5.4 on perilesional biopsy.
- New text additions throughout section 6 with special attention to section 6.1 treatment modalities and new summary of evidence in section 6.2.5 on active surveillance strategy as well as 6.4.2 on controversies in the definitions of clinically relevant PSA relapse. Substantial text additions to section 6.7.6.6 on combinations with PARP inhibitors
- New recommendation in section 6.3.2.5 Guidelines for the treatment of intermediate-risk disease regarding active surveillance and radiotherapeutic treatment.
- New recommendations in section 6.3.3.4 Guidelines for radical and palliative treatment of high-risk localised disease and for Pelvic lymph node dissection (PLND) and radiotherapeutic treatment
- New recommendations in section 6.7.13 on the Guidelines for systemic treatments of castrate-

resistant disease.
- Small amendments to Figure 6.4 and Figure 6.5
- New subsection 8.2.1 on active surveillance and 8.2.5.8 on osteonecrosis during bisfosfonates or denosumab as well as substantial addition of text to section 8.3.1 and 8.3.2

2. METHODS

2.1 Data identification

For the 2024 PCa Guidelines, new and relevant evidence has been identified, collated and appraised through a structured assessment of the literature. A number of comprehensive searches were performd, covering all sections of the PCa Guidelines. The search was limited to English language publications. Databases searched included Medline, EMBASE and the Cochrane Libraries, covering a time frame between April 1st 2022 and May 1st 2023. A total of 3233 unique records were identified, retrieved and screened for relevance. A detailed search strategy is available online: https://uroweb.org/guideline/prostate-cancer/?type=appendices-publications.

Changes in recommendations were generally only considered on the basis of high-level evidence (i.e. systematic reviews (SR) with meta-analysis, randomised controlled trials (RCTs), and prospective comparative studies) published in the English language. Additional information can be found in the general Methodology section of this print and online at the EAU website: https://uroweb.org/guidelines/policies-and-methodological-documents/.

Recommendation within the Guidelines are developed by the panels to prioritise clinically important care decisions. The strength of each recommendation is determined by the balance between desirable and undesirable consequences of alternative management strategies, the quality of the evidence (including certainty of estimates), and the nature and variability of patient values and preferences. This decision process, which can be reviewed in the strength rating forms which accompany each guideline statement, addresses a number of key elements:
:

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

Strong recommendations typically indicate a high degree of evidence quality and/or a favourable balance of benefit to harm and patient preference. Weak recommendations typically indicate availability of lower quality evidence, and/or equivocal balance between benefit and harm, and uncertainty or variability of patient preference [4]. The strength rating forms will be available online.

A list of Associations endorsing the EAU Guidelines can also be viewed online at the above address. In addition, the International Society of Geriatric Oncology (SIOG), the European Society for Radiotherapy & Oncology (ESTRO), the European Society for Urogenital Radiology (ESUR), the European Association of Nuclear Medicine (EANM) and the International Society of Urological Pathology (ISUP) have endorsed the PCa Guidelines.

2.2 Review

Publications ensuing from SRs have all been peer-reviewed.

2.3 Future goals

Results of ongoing and new SRs will be included in the 2025 update of the PCa Guidelines:

- A SR assessing the performance of risk stratification tools incorporating imaging, biomarkers, biopsy involvement and/or magnetic resonance imaging (MRI)-targeted biopsies, compared to the classical risk classifications (d'Amico, EAU, the Cancer of the Prostate Risk Assessment (CAPRA) and the National Comprehensive Cancer Network (NCCN)) recommended in current guidelines for predicting biochemical recurrence, metastasis or death after local treatment for prostate cancer. Are the new stratification tools preferred above the classical risk classifications?
- A SR assessing the outcomes of brachytherapy (BT) boost combined with external beam RT for PCa.
- Care pathways for the various stages of PCa management have been developed. These pathways will, in due time, inform treatment flowcharts and an interactive app.

3. EPIDEMIOLOGY AND AETIOLOGY

3.1 Epidemiology

Prostate cancer (PCa) is the second most commonly diagnosed cancer in men, with an estimated 1.4 million diagnoses and 375,000 deaths worldwide in 2020 [5, 6]. In Europe, it is the most frequently diagnosed cancer in men and the third cancer-related cause of death in men [7].

A SR of autopsy studies reported a prevalence of PCa at age < 30 years of 5% (95% confidence interval [CI]: 3–8%), increasing by an odds ratio (OR) of 1.7 (1.6–1.8) per decade, to a prevalence of 59% (48–71%) by age > 79 years [8]. There is variation in the frequency of autopsy-detected PCa between men with different ethnical backgrounds and geographical areas (e.g., 83% in white US males vs. 41% in Japan at age 71–80) [9].

Regarding incidence of PCa diagnosis, the variation is even more pronounced between different geographical areas, driven by rate of prostate-specific antigen (PSA) testing and influenced by (inter)national organisations recommendations on screening (see Section 5.1) [10]. It is highest in Australia/New Zealand and Northern America (age-standardised rates [ASR] per 100,000 of 111.6 and 97.2, respectively), and in Western and Northern Europe (ASRs of 94.9 and 85, respectively). The incidence is low in Eastern and South-Central Asia (ASRs of 10.5 and 4.5, respectively), but rising [11]. Rates in Eastern and Southern Europe were low but have also shown a steady increase [6, 9]. Besides PSA testing, incidence is also dependent on the age of the population, geography and ethnicity.

There is relatively less variation in mortality rates worldwide, although rates are generally high in populations of African descent (e.g., Caribbean: ASR of 29 and Sub-Saharan Africa: ASRs ranging between nineteen and fourteen), intermediate in the USA and very low in Asia (South-Central Asia: ASR of 2.9) [6, 12]. Mortality due to PCa has decreased in most Western nations but the magnitude of the reduction varies between countries [5].

3.2 Aetiology

*3.2.1 **Family history/hereditary prostate cancer***

Family history and ethnic background are associated with an increased PCa incidence suggesting a genetic predisposition [13, 14]. Men of African ancestry in the Western world demonstrate more unfavourable outcomes due to a combination of biological, environmental, social, and health care factors [15]. They are more likely to be diagnosed with more advanced disease [16] and upgrade after prostatectomy was more frequent as compared to Caucasian men (49% vs. 26%) [17]. Racial disparities in development of, prevention of, and therapies for PCa may exist. Indeed, a multi-ancestry polygenic risk score of 278 risk variants published by Chen et. al. showed a strong association with PCa risk in men with African ancestry and might be used to identify susceptibility in this high-risk population [18]. It should be kept in mind that many PCa studies include either small percentages of men from other origin than Caucasians or focus on highly specific other groups [19].

However, only a small subpopulation of men with PCa have true hereditary disease (≥ 3 cases in the same family, PCa in three successive generations, or ≥ two men diagnosed with PCa < 55 yrs). Hereditary PCa (HPCa) is associated with a six-to-seven-year earlier disease onset but the disease aggressiveness and clinical course does not seem to differ in other ways [13, 20]. In a large USA population database, HPCa (reported by 2.18% of participants) showed a relative risk (RR) of 2.30 for diagnosis of any PCa, 3.93 for early-onset PCa, 2.21 for lethal PCa, and 2.32 for clinically significant PCa (csPCa) [21]. These increased risks with HPCa were higher than for familial PCa (≥two first- or second-degree relatives with PCa on the same side of the pedigree), or familial syndromes such as hereditary breast- and ovarian cancer and Lynch syndrome. With the father as well as two brothers affected, the probability of high-risk PCa at age 65 was 11.4% (vs. a population risk of 1.4%), and for any PCa 43.9% vs. 4.8%, in a Swedish population-based study [22].

3.2.1.1 Germline mutations and prostate cancer

Genome-wide association studies have identified more than 100 common susceptibility loci contributing to the risk for (aggressive) PCa [23, 24]. The frequency and distribution of positive germline variants in 3,607 unselected PCa patients showed that 620 (17.2%) contained a pathogenic mutation [25]. Whilst in men with PCa disease undergoing multigene testing across the USA, it was found that 15.6% of men with PCa have pathogenic variants identified in genes tested ([Breast Cancer genes] *BRCA1, BRCA2, HOXB13, MLH1, MSH2, PMS2, MSH6, EPCAM, ATM, CHEK2, NBN,* and *TP53*), and 10.9% of men have germline pathogenic variants in DNA repair genes (see Table 3.1) [26]. Pathogenic variants were most commonly identified in *BRCA2* (4.5%), *CHEK2* (2.2%), *ATM* (1.8%), and *BRCA1* (1.1%) [26].

Among men with metastatic PCa, an incidence of 11.8% was found for germline mutations in genes mediating DNA-repair processes [27] and 16.2% of patients diagnosed with metastatic castrate-resistant PCa (mCRPC) [28]. Targeted genomic analysis of genes associated with an increased risk of PCa could offer options to identify families at high risk [29, 30].

A prospective cohort study of male *BRCA1* and *BRCA2* carriers confirmed *BRCA2* association with aggressive PCa [31]. An analysis of the outcomes of 2,019 patients with PCa (18 *BRCA1* carriers, 61 *BRCA2* carriers, and 1,940 non-carriers) showed that PCa with germline *BRCA1/2* mutations were more frequently associated with ISUP grade group ≥ 4, T3/T4 stage, nodal involvement, and metastases at diagnosis than PCa in non-carriers [32]. *BRCA*-susceptibility gene mutation carriers were also reported to have worse outcome when compared to non-carriers after local therapy [33]. In a retrospective study of 313 patients who died of PCa and 486 patients with low-risk localised PCa, the combined *BRCA1/2* and *ATM* mutation carrier rate was significantly higher in lethal PCa patients (6.07%) than in localised PCa patients (1.44%) [34]. The rate of PCa among *BRCA1* carriers was more than twice as high (8.6% vs. 3.8%) compared to the general population, in contrast to findings of the prospective IMPACT study (Identification of Men with a Genetic Predisposition to Prostate Cancer (see Chapter 5) [35].

Table 3.1: Germline mutations in DNA repair genes associated with increased risk of prostate cancer

Gene	Location	Prostate cancer risk	Findings
BRCA2	13q12.3	- RR 2.5 to 4.6 [39, 40] - PCa at 55 years or under: RR: 8–23 [36, 37]	• up to 12 % of men with metastatic PCa harbour germline mutations in 16 genes (including *BRCA2* [5.3%]) [27] • 2% of men with early-onset PCa harbour germline mutations in the *BRCA2* gene [36] • *BRCA2* germline alteration is an independent predictor of metastases and worse PCa-specific survival [32, 38]
ATM	11q22.3	RR: 6.3 for metastatic PCa [27]	• higher rates of lethal PCa among mutation carriers [34] • up to 12% of men with metastatic PCa harbour germline mutations in 16 genes (including *ATM* [1.6%]) [27]
CHEK2	22q12.1	OR 3.3 [39, 40]	• up to 12% of men with metastatic PCa harbour germline mutations in 16 genes (including *CHEK2* [1.9%]) [27]
BRCA1	17q21	RR: 1.8–3.8 at 65 years or under [41, 42]	• higher rates of lethal PCa among mutation carriers [34] • up to 12% of men with metastatic PCa harbour germline mutations in 16 genes (including *BRCA1* [0.9%]) [27]
HOXB13	17q21.2	OR 3.4–7.9 [29, 43]	• significantly higher PSA at diagnosis, higher Gleason score and higher incidence of positive surgical margins in the radical prostatectomy specimen than non-carriers [44]
MMR genes *MLH1* *MSH2* *MSH6* *PMS2*	3p21.3 2p21 2p16 7p22.2	RR: 3.7 [45]	• Mutations in *MMR* genes are responsible for Lynch syndrome [46] • *MSH2* mutation carriers are more likely to develop PCa than other *MMR* gene mutation carriers [47]

BRCA2 = breast cancer gene 2; ATM = ataxia telangiectasia mutated; CHEK2 = checkpoint kinase 2; BRCA1 = breast cancer gene 1; GS = Gleason score; HOXB13 = homeobox B13; MMR = mismatch repair; MLH1 = mutL homolog 1; MSH2 = mutS homolog 2; MSH6 = mutS homolog 6; OR = odds ratio; PMS2 = post-meiotic segregation increased 2; PCa = prostate cancer; RP = radical prostatectomy; RR = relative risk; PSA = prostate-specific antigen.

*3.2.2 **Risk factors for prostate cancer***

A wide variety of exogenous/environmental factors have been discussed as being associated with the risk of developing PCa or as being aetiologically important for the progression from latent to clinical PCa [48]. Asians who immigrated to the USA have approximately half the risk of PCa when compared to their US born Asian-descendant counterparts, implying a role for environmental or dietary factors [49]. However, currently there are no known effective preventative dietary or pharmacological interventions.

3.2.2.1 Metabolic syndrome

The single components of metabolic syndrome (MetS) that have been associated with a significantly greater risk of PCa are hypertension (p = 0.035) and waist circumference ≥ 102 cm (p = 0.007), but in contrast, having ≥ 3 components of MetS is associated with a reduced risk (OR: 0.70, 95% CI: 0.60–0.82) [50, 51].

3.2.2.1.1 Obesity

Within the Reduction by Dutasteride of Prostate Cancer Events (REDUCE) study, obesity was associated with lower risk of low-grade PCa (OR: 0.79, p = 0.01), and a higher risk of high-grade PCa (OR: 1.28, p = 0.042), in multivariable analyses [52]. This effect seems mainly explained by environmental determinants of height/body mass index (BMI) rather than genetically elevated height or BMI [53]. A SR showed an association between obesity and increased PC-specific mortality [54].

3.2.2.1.2 Diabetes/metformin

The association between metformin use and PCa is controversial. At population level, metformin users (but not other oral hypoglycaemic agents) were found to be at a decreased risk of PCa diagnosis compared with never users (adjusted OR: 0.84, 95% CI: 0.74–0.96) [55]. In 540 diabetic participants of the REDUCE study, metformin use was not significantly associated with PCa and therefore not advised as a preventive measure (OR: 1.19, p = 0.50).

3.2.2.1.3 Cholesterol/statins

A meta-analysis of fourteen large prospective studies did not show any association between blood total cholesterol, high-density lipoprotein cholesterol, low-density lipoprotein cholesterol levels and the risk of developing either overall PCa or high-grade PCa [51]. Results from the REDUCE study did not show a preventive effect of statins on PCa risk, even though a meta-analysis suggested a lower risk of advanced PCa in statin users [50, 56].

3.2.2.2 Dietary factors

The association between a wide variety of dietary factors and PCa have been studied, but there is a paucity of quality evidence (Table 3.2). To date, the current body of evidence will not support a causal relationship between specific (dietary and otherwise) factors and the development of PCa. Consequently, no effective preventative strategies can be suggested.

Table 3.2: Main dietary factors that have been associated with PCa

Alcohol	High alcohol intake, but also total abstention from alcohol has been associated with a higher risk of PCa and PCa-specific mortality [57]. A meta-analysis shows a dose-response relationship with PCa [58].
Coffee	Coffee consumption may be associated with a reduced risk of PCa; with a pooled RR of 0.91 for the highest category of coffee consumption [59].
Dairy	A weak correlation between high intake of protein from dairy products and the risk of PCa was found [60].
Fat	No association between intake of long-chain omega-3 poly-unsaturated fatty acids and PCa was found [61]. A relation between intake of fried foods and risk of PCa may exist [62].
Tomatoes (lycopenes/ carotenes)	A trend towards a favourable effect of tomato intake (mainly cooked) and lycopenes on PCa incidence has been identified in meta-analyses [68, 69]. Randomised controlled trials comparing lycopene with placebo did not identify a significant decrease in the incidence of PCa [63].
Meat	Meta-analyses show a potential association between red meat, total meat, and processed meat consumption and PCa [64, 65].

Soy (phytoestrogens [isoflavones/ coumestans])	Phytoestrogen intake was significantly associated with a reduced risk of PCa in a meta-analysis [66]. Total soy food intake has been associated with a reduced risk of PCa, but also with an increased risk of advanced disease [67, 68].
Vitamin D	A U-shaped association has been observed, with both low- and high vitamin-D concentrations being associated with an increased risk of PCa, and more strongly for high-grade disease [68, 69].
Vitamin E/Selenium	An inverse association of blood, but mainly nail selenium levels (reflecting long-term exposure) with aggressive PCa have been found [70, 71]. Selenium and Vitamin E supplementation were, however, found not to affect PCa incidence [72].

3.2.2.3 Hormonally active medication

3.2.2.3.1 5-alpha-reductase inhibitors (5-ARIs)

Although it seems that 5-ARIs have the potential of preventing or delaying the development of PCa (decreasing the risk by 25% but only for ISUP grade group 1 cancer), this must be weighed against treatment-related side effects as well as the potential small increased risk of high-grade PCas (although this does not seem to impact PCa mortality) [73, 74]. None of the available 5-ARIs have been approved by the European Medicines Agency (EMA) for chemoprevention.

3.2.2.3.2 Testosterone

Hypogonadal men receiving testosterone supplements do not have an increased risk of developing PCa [75]. A pooled analysis showed that men with very low concentrations of free testosterone (lowest 10%) have a below average risk (OR: 0.77) of PCa [76]. Furthermore, although the evidence is limited, men who are managed expectantly for PCa, or who received radical curative therapy, do not have worse outcomes when receiving testosterone supplementation, despite a theoretical higher risk of progression after correction of the hypogonadal situation [77].

3.2.2.4 Other potential risk factors

A significantly higher rate of ISUP grade group ≥ 2 PCa (hazard ratio [HR]: 4.04) was found in men with inflammatory bowel disease when compared with the general population [78]. Balding was associated with a higher risk of PCa death [79]. Gonorrhoea was significantly associated with an increased incidence of PCa (OR: 1.31, 95% CI: 1.14–1.52) [80]. Occupational exposure may also play a role, based on a meta-analysis which revealed that night-shift work is associated with an increased risk (2.8%, p = 0.030) of PCa [81]. Current cigarette smoking was associated with an increased risk of PCa death (RR: 1.24, 95% CI: 1.18–1.31) and with aggressive tumour features and worse prognosis, even after quitting smoking [82, 83]. A meta-analysis on Cadmium (Cd) found a positive association (magnitude of risk unknown due to heterogeneity) between high Cd exposure and risk of PCa for occupational exposure, but not for non-occupational exposure, potentially due to higher Cd levels during occupational exposure [84]. Men positive for human papillomavirus-16 may be at increased risk [85]. Plasma concentration of the estrogenic insecticide chlordecone is associated with an increase in the risk of PCa (OR: 1.77 for highest tertile of values above the limit of detection) [86]. A number of other factors previously linked to an increased risk of PCa have been disproved including vasectomy [87] and self-reported acne [88]. There are conflicting data about the use of aspirin or nonsteroidal anti-inflammatory drugs and the risk of PCa and mortality [89, 90]. Ultraviolet radiation exposure decreased the risk of PCa (HR: 0.91, 95% CI: 0.88–0.95) [91]. A review found a small but protective association of circumcision status with PCa [92]. Higher ejaculation frequency (≥ 21 times a month vs. 4 to 7 times) has been associated with a 20% lower risk of PCa [93].

*3.2.3 **Summary of evidence for epidemiology and aetiology***

Summary of evidence	**LE**
Prostate cancer is a major health concern in men, with incidence mainly dependent on age and extent of PSA testing.	3
Genetic factors are associated with risk of (aggressive) PCa.	3
A variety of dietary/exogenous/environmental factors have been associated with PCa incidence and prognosis.	3
In hypogonadal men, testosterone supplements do not increase the risk of PCa.	2a
No conclusive data exist which could support specific preventive or dietary measures aimed at reducing the risk of developing PCa.	1a

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 discussion about prognosis with patients, the design of clinical trials on relatively homogeneous populations, the comparison of clinical and pathological data obtained from different hospitals across the world, and the development of recommendations for the treatment of these patient populations. Throughout these Guidelines the Union for International Cancer Control (UICC) 8th edition (2017), the Tumour, Node, Metastasis (TNM) classification for staging of PCa (Table 4.1) [94] and the EAU risk group classification are used [95]. The latter classification is based on the grouping of patients with a similar risk of biochemical recurrence (BCR) after radical prostatectomy (RP) or external beam radiotherapy (EBRT). Changes in the diagnostic pathway, such as imaging (e.g., MRI, Prostate-Specific Membrane Antigen [PSMA] Positron Emission Tomography Computed Tomography [PET/CT] scan) and biopsy (e.g., increasing number of systematic biopsy cores, targeted biopsy) may cause a stage shift in risk classification systems [96].

Although the 2017 American Joint Committee on Cancer (AJCC) staging 8th edition specifically states that clinical staging should be based on digital rectal examination (DRE) only, such an explicit comment is not made by the UICC. Since clinical stage as assessed by DRE only, is included in the EAU (D'Amico) risk group classification, cT-stage should be based on DRE findings and not on imaging. Additional staging information based on imaging should be reported separately. A non-palpable PCa with bilateral positive biopsies and extra-prostatic extension (EPE) on MRI would therefore be categorised as cT1c with a separate report of MRI findings.

Table 4.1: Clinical Tumour Node Metastasis (TNM) classification of PCa [94]

T - Primary Tumour (stage based on digital rectal examination [DRE] only)	
TX	Primary tumour cannot be assessed
T0	No evidence of primary tumour
T1	Clinically inapparent tumour that is **not palpable**
T1a	Tumour incidental histological finding in 5% or less of tissue resected
T1b	Tumour incidental histological finding in more than 5% of tissue resected
T1c	Tumour identified by needle biopsy (e.g. because of elevated prostate-specific antigen [PSA])
T2	Tumour that is palpable and confined within the prostate
T2a	Tumour involves one half of one lobe or less
T2b	Tumour involves more than half of one lobe, but not both lobes
T2c	Tumour involves both lobes
T3	Tumour extends **palpably** through the prostatic capsule
T3a	Extracapsular extension (unilateral or bilateral)
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 (pelvic) Lymph Nodes[1]	
NX	Regional lymph nodes cannot be assessed
N0	No regional lymph node metastasis
N1	Regional lymph node metastasis
M - Distant Metastasis[2]	
M0	No distant metastasis
M1	Distant metastasis
M1a	Non-regional lymph node(s)
M1b	Bone(s)
M1c	Other site(s)

[1] *Metastasis no larger than 0.2 cm can be designated pNmi.*

[2] *When more than one site of metastasis is present, the most advanced category is used. (p)M1c is the most advanced category.*

Pathological staging (pTNM) is based on histopathological tissue assessment and largely parallels the clinical TNM, except for clinical T1 and T2 substages. Pathological stages pT1a/b/c do not exist and histopathologically confirmed organ-confined PCas after RP are pathological stage pT2. The current UICC no longer recognises pT2 substages [94].

Of note: the EANM recently proposed a molecular imaging TNM ('miTNM') classification, taking into account PSMA PET/CT findings [97]. The prognosis of the miT, miN and miM substages is likely to be better than their T, N and M counterparts due to the 'Will Rogers phenomenon'; the extent of this prognosis shift remains to be assessed as well as its practical interest and impact [98]. This reclassification is not endorsed by the UICC or the AJCC.

4.2 Gleason score and International Society of Urological Pathology 2019 grade

In the original Gleason grading system, 5 Gleason grades (ranging from 1–5) based on histological tumour architecture were distinguished, but in the 2005 and subsequent 2014 ISUP consensus meetings Gleason grades 1 and 2 were eliminated [99, 100]. The 2005 ISUP modified Gleason score (GS) of biopsy-detected PCa comprises the Gleason grade of the most extensive (primary) pattern, plus the second most common (secondary) pattern, if two are present. If only one pattern is present, it needs to be doubled to yield the GS. For three grades, the biopsy GS comprises the most common grade plus the highest grade, irrespective of its extent. In case intraductal carcinoma (IDC) is present intermixed with invasive PCa, it should be incorporated in the GS based on its underlying architectural pattern [101]. In addition to reporting of the carcinoma features for each biopsy side, an overall (or global) GS based on the carcinoma-positive biopsies can be provided. The global GS takes into account the cumulative extent of each grade from all prostate biopsies. The 2014 and 2019 ISUP endorsed a grading system limiting the number of PCa grades, ranging them from 1 to 5 (see Table 4.2) [100, 102].

Table 4.2: International Society of Urological Pathology 2014 grade (group) system

Gleason score	ISUP grade
2-6	1
7 (3+4)	2
7 (4+3)	3
8 (4+4 or 3+5 or 5+3)	4
9-10 (4+5 or 5+4 or 5+5)	5

4.3 Clinically significant prostate cancer

The descriptor 'clinically significant' is widely used to differentiate PCa that may cause morbidity or death in a specific patient from types of PCa that rarely do. This distinction is particularly important as insignificant PCa is common [8]. Unless this distinction is made, such cancers are at high risk of being over-treated, with the treatment itself risking harmful side effects to patients. The over-treatment of insignificant PCas has also been criticised as a major drawback of population-based screening and individual early detection [103]. Although pathological factors are often used to delineate insignificant PCa, the definition of significant vs. insignificant is a balance between tumour and patient factors. High-risk PCa is significant in almost all men, except when life expectancy is limited. Low-risk PCa is insignificant in almost all men.

From a pathological point of view, in large studies of RP specimens with only ISUP grade group 1 disease, EPE (0.3%) [104] and biochemical recurrence (3.5%) were rare, and seminal vesicle (SV) invasion or lymph node (LN) metastasis did not occur at all [105, 106]. International Society of Urological Pathology grade group 1 disease at RP itself can therefore be considered clinically insignificant. Whilst ISUP grade group 1 bears the hallmarks of cancer histologically, ISUP grade group 1 at RP itself does not behave in a clinically malignant fashion [107]. It is important to note that the studies showing absence of metastasis in ISUP grade group 1 were all done on RP specimens; ISUP grade group 1 on biopsy is associated with a low risk of developing metastasis and disease-specific death, due to under-sampling of a higher-grade component. In a contemporary retrospective study of men with cT1-T2 cN0 ISUP grade group 1 PCa at mpMRI-targeted biopsy, 72% had ISUP grade group ≥ 2, 9% ISUP grade group ≥ 3, 25% had pT3a and 4% pT3b at subsequent RP [108]. Finally, modifications in PCa grading has led to a grade shift during the past ten to fifteen years; for instance the introduction of the ISUP 2005 led to 20% of pre-ISUP 2005 GS 6 tumours being upgraded to GS 7 or higher, which has to be taken into account when interpreting older studies [109].

The current standard practice of MRI-targeted and template biopsies has improved diagnostic accuracy [110], however sampling error may still occur such that higher grade cancer could be missed. This should especially be considered in case of high PSA density, high pathological biopsy tumour volume and a visible lesion at MRI, but only ISUP grade group 1 at biopsy [111, 112]. Another complexity in defining insignificant cancer is that ISUP grade group 1 may progress to higher grades over time, becoming clinically significant at a later biopsy [113].

Therefore, although ISUP grade group 1 itself can be described as clinically insignificant, it is important to take into account other factors, including age, imaging prior to biopsy and adequate sampling core number. When combined with low-risk clinical factors (see Table 4.3), ISUP grade group 1 represents low-risk PCa and recommended management options are active surveillance (AS) or watchful waiting (WW) (see Sections 6.2.1.1 & 6.2.1.2). It has been proposed to rename ISUP grade group 1 "tumours" omitting the "cancer" label [114, 115]. At this moment, no broad consensus yet exists for changing this disease taxonomy [116, 117]. Instead, although it is probably insignificant cancer, it should be appropriately observed.

Epidemiological and autopsy data suggest that a proportion of ISUP grade group 2 PCa would remain undetectable during a man's life [118] and therefore may be over-treated. In current guidelines deferred treatment may be offered to select patients with intermediate-risk PCa [119], but clear evidence is lacking for appropriate selection criteria [120].

Recent papers have defined clinically significant cancer differently, commonly using ISUP grade group 2 and above and even ISUP grade group 3 and above, demonstrating the lack of consensus and evolution of its definition [121, 122]. Some papers provide more than one definition within a single study [123, 124]. Since there is insufficient data to relate modern histological grading to hard clinical endpoints, it is imperative that authors define and state in their own studies what they believe csPCa is, including exactly how the disease was diagnosed.

Table 4.3: EAU risk groups for biochemical recurrence of localised and locally-advanced prostate Cancer (based on systematic biopsy)

Definition			
Low-risk	**Intermediate-risk**	**High-risk**	
PSA < 10 ng/mL and GS < 7 (ISUP grade 1) and cT1-2a*	PSA 10–20 ng/mL or GS 7 (ISUP grade 2/3) or cT2b*	PSA > 20 ng/mL or GS > 7 (ISUP grade 4/5) or cT2c*	any PSA any GS (any ISUP grade) cT3-4 or cN+**
Localised			**Locally advanced**

GS = Gleason score; ISUP = International Society for Urological Pathology; PSA = prostate-specific antigen.
**** Based on digital rectal examination.***
***** Based on CT/bone scan.***

4.4 Prognostic relevance of stratification

Tumour, Node, Metastasis (TNM) staging is a schematic representation of anatomic tumour extent and pathological grade is reflective of intrinsic features of tumour aggressiveness. EAU risk group classification, which is essentially based on D'Amico's classification system for PCa, combines clinical information on tumour extent, PSA and pathology from systematic biopsy (Table 4.3). A more precise stratification of the clinically heterogeneous subset of intermediate-risk group patients could provide a better framework for their management [125, 126]. Specifically, the NCCN Guidelines subdivide intermediate-risk disease into favourable and unfavourable intermediate-risk, with unfavourable features including ISUP grade group 3, and/or ≥ 50% positive systematic biopsy cores and/or at least two intermediate-risk factors [119]. In 2016 Cambridge Prognostic Groups representing a 5-tier model based on ISUP grade group, PSA and cT-stage were shown to have significantly better discriminative performance than current 3-tier EAU risk groups for prostate cancer specific mortality [127]. This model separates both EAU intermediate- and high-risk groups in clinically relevant subgroups and has been validated in several cohorts [127-129].

4.5 Guidelines for classification and staging systems

Recommendations	Strength rating
Use the Tumour, Node, Metastasis (TNM) classification for staging of PCa.	Strong
Clinical stage should be based on digital rectal examination (DRE) only; additional staging information based on imaging should be reported separately.	Strong
Use the International Society of Urological Pathology (ISUP) 2019 system for grading of PCa.	Strong

5. DIAGNOSTIC EVALUATION

5.1 Screening and individual early detection

The diagnostic pathway for PCa aims for timely detection of significant PCa, while leaving insignificant PCa undetected, balancing diagnostic accuracy with the burden on an individual and healthcare provider. Patient-specific factors such as lower urinary tract symptoms (LUTS), family history, age, and comorbidity should always be considered.

Men may enter the diagnostic pathway through different indications, including clinical symptoms, opportunistic early detection (individual), or screening (population-based). The prevalence of PCa and significant PCa is different dependent on the indication, resulting in different yields of the subsequent diagnostic pathway.

5.1.1 Clinical Symptoms

Localised PCa is usually asymptomatic. Local progression may cause symptoms such as LUTS, erectile dysfunction (ED), retention, pain, or haematuria. Bone metastases may cause pain or spinal cord compression. Digital rectal examination (DRE) and PSA are usually part of the initial diagnostic work-up in these cases, after which a further diagnostic algorithm may be initiated. Definitive diagnosis normally depends on histopathological verification in prostate biopsy cores. However, men with high suspicion of malignancy (e.g. malignant feeling prostate, PSA >100 ng/mL and a positive bone scan might avoid a biopsy especially if pre-existing comorbidities would exclude second-line treatments.

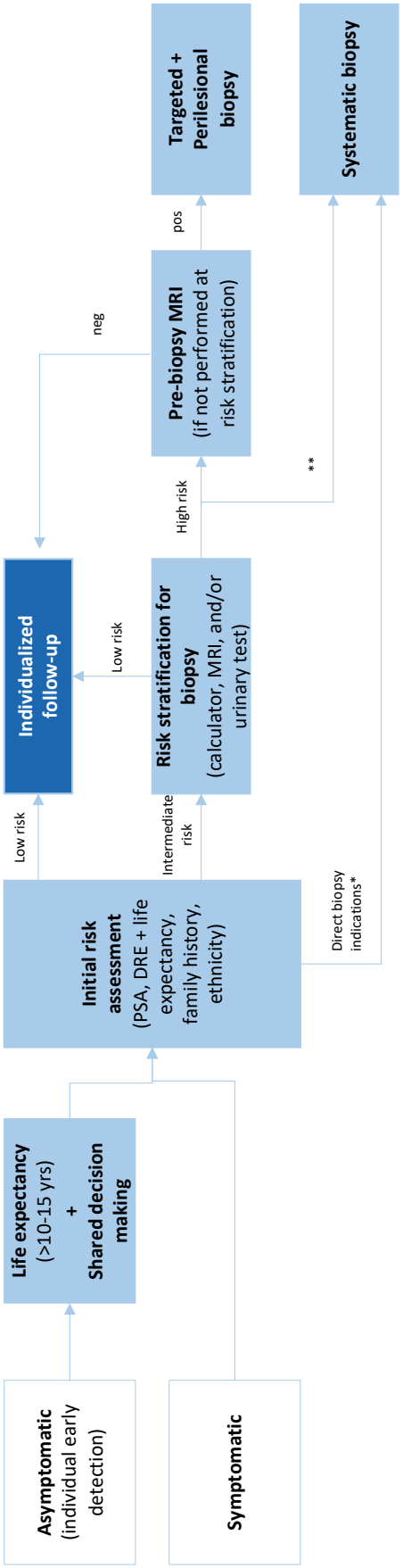
5.1.2 Individual early detection

Early detection may be initiated on an individual level. Men with risk factors include age > 50 years; men from 45 years of age with a family history of PCa; men of African descent from 45 years of age; men carrying *BRCA2* mutations from 40 years of age [130, 131]. The risk of detecting clinically insignificant cancers and possible overtreatment should be discussed along with the possibility of improved disease-specific mortality. It is difficult to accurately estimate the individual benefit or harm due to early detection for the individual man but the effect may be larger as diluting effects from intention-to-treat analyses in screening trials are not applicable (i.e. non-participation: no participation after screening invitation; contamination: screening occurring in control arm) [132]. Nevertheless, 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 only a marginal survival benefit, at best, in the opportunistic screening regimen [133].

Baseline PSA may be used to predict PCa mortality after fifteen to twenty yrs. Follow-up intervals of two years may be offered to those initially at risk (PSA > 1 ng/mL at 40 years; PSA > ng/mL at 60 years) [134, 135].

The age at which attempts an early diagnosis should be stopped remains controversial, but an individual's life expectancy must definitely be taken into account. Men who have less than a fifteen-year life expectancy are unlikely to benefit, based on data from the Prostate Cancer Intervention Versus Observation Trial (PIVOT) and the European Randomized Screening for Prostate Cancer (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 6.1 'Estimating life expectancy and health status' and in the SIOG Guidelines [136]. Informed men with one of the risk factors above, a life expectancy of > fifteen years and requesting investigation should be given a PSA test and undergo a DRE, after which a further diagnostic algorithm may be initiated [137].

Figure 5.1 Presents a flow diagram for deciding on prostate biopsy



* PSA >50, cT3-4
** If MRI not available / possible

5.1.3 Population-based screening

Population or mass screening is defined as the 'systematic examination of asymptomatic men to identify individuals at risk for a specific disease' and is usually initiated by health authorities. The co-primary objectives are:

- reduction in mortality due to PCa;
- a maintained quality of life (QoL) as expressed by QoL-adjusted gain in life years (QALYs).

Screening for PCa remains one of the most controversial topics in the urological literature [138]. A Cochrane review of randomised PCa screening trials with PCa mortality as endpoint was published in 2013 [139] and updated in 2018 [140, 141]. The main findings of the updated publication from the results of five RCTs, randomising more than 721,718 men, are:

- Screening is associated with an increased diagnosis of PCa (Incidence ratio [IR]: 1.23 95% CI: 1.03–1.48).
- Screening is associated with detection of more localised disease (RR: 1.39, [1.09–1.79]) and less advanced PCa (T3–4, N1, M1; RR: 0.85 [0.72–0.99]).
- No PCa-specific survival benefit was observed (IR: 0.96 [0.85–1.08]). This was the main endpoint in all trials.
- No overall survival (OS) benefit was observed (IR: 0.99, 95% CI: 0.98–1.01). None of the trials were designed/powered for this endpoint.

The included studies are different regarding multiple aspects including trial size, time periods, age groups, participation/compliance rates, previous screening rates (opportunistic testing in control arm, 'contamination'), one-time vs. repeat screening, and the applied diagnostic pathway. These differences account for discrepancies in results between single studies and the Cochrane review aggregated findings.

The ERSPC study started in the early 90's, included >182,000 European men, found a significant reduction in PCa mortality due to screening. ERSPC applied a mainly PSA-based screening protocol (cut-off 3.0–4.0 ng/mL followed by systematic sextant prostate biopsy, every two to four years in men aged 50–74) [142] The contamination rate was relatively low when compared to other large studies such as the Prostate Lung Colorectal and Ovarian (PLCO) screening trial [142]. A limitation is the heterogeneity in patient groups and the applied screening protocols. Since 2013, data have been updated with sixteen years of follow-up [142]. With extended follow-up, the mortality reduction (21% and 29% after non-compliance adjustment) remains unchanged. However, the number needed to screen (NNS) and to treat is decreasing and is now below the NNS observed in breast cancer trials [142, 143] (Table 5.1).

Table 5.1: Follow-up data from the ERSPC study [142]

Years of follow-up	Number needed to screen	Number needed to treat
9	1,410	48
11	979	35
13	781	27
16	570	18

In the Rotterdam section of the ERSPC, with 21 years follow-up, the risk ratio of death due to PCa was 0.73 in the screening group, with number needed to invite of 246 and number needed to diagnose (NND) of fourteen to prevent one death due to PCa [144]. To prevent one metastasized case NNS was 121 and NND seven.

In the Goteborg screening trial, with eighteen years of follow-up, the ratio of death from PCa for the screening group compared with the control group was 0.65 (95% CI: 0.49–0.87) and for men starting screening at age 55–59 it was 0.47 (95% CI: 0.29–0.78) [145]. The number needed to invite was 231; the NND ten.

The benefit of screening in reducing PCa-specific mortality (PCSM) and the even more favourable impact on metastases rates, is counter-balanced by the side effects of screening such as increased diagnosis rates, which has led to over-treatment of low-risk PCa, and subsequent treatment-related side-effects [146]. Regarding QoL, the beneficial effects of screening and the side effects seem to balance out, resulting in limited overall impact on the invited population [146, 147].

Recognition of the harms of over-diagnosis and over-treatment had led to a redesign in the pathway for early detection of PCa including identification of specific risk groups, individualised re-testing interval, improved indication for biopsy using risk calculators and/or MRI, targeted biopsies, and the application of AS for low-risk disease.

After a negative screening, PSA measurement and DRE need to be repeated [148], but the optimal intervals for PSA testing and DRE follow-up are unknown as they varied between several prospective screening trials. A risk-adapted strategy might be a consideration, based on the initial PSA level. Men with a baseline PSA < 1 ng/mL at 40 years or < 2 ng/mL at 60 years are at decreased risk of PCa metastasis or death from PCa several decades later [46, 135]. The retesting interval can therefore be every two years for those initially at increased risk or postponed up to eight years for those at low-risk [149].

An analysis of ERSPC data supports a recommendation for an eight-year screening interval in men with an initial PSA concentration < 1 ng/mL; fewer than 1% of men with an initial PSA concentration < 1 ng/mL were found to have a concentration above the biopsy threshold of 3 ng/mL at four-year follow-up; the cancer detection rate by eight years was close to 1% [150]. The long-term survival and QoL benefits of extended PSA re-testing (every eight years) remain to be proven at a population level.

5.1.4 Screening in patients with BRCA mutations

The IMPACT study evaluates targeted PCa screening using PSA in men aged 40–69 years with germline *BRCA1/2* mutations (annually, biopsy recommended if PSA > 3.0 ng/mL). After three years of screening, *BRCA2* mutation carriers were associated with a higher incidence of PCa, a younger age of diagnosis, and more clinically significant tumours compared with non-carriers [131, 151]. The influence of *BRCA1* mutations on PCa remained unclear. No differences in age or tumour characteristics were detected between *BRCA1* carriers and *BRCA1* non-carriers. The mismatch repair cohort of IMPACT in men with MSH2 and MSH6 pathogenic variants found a higher incidence of significant PCa vs. non-carriers [152].

5.1.5 Guidelines for individual early detection

Recommendations	Strength rating
Do not subject men to prostate-specific antigen (PSA) testing without counselling them on the potential risks and benefits.	Strong
Offer an individualised risk-adapted strategy for early detection to a well-informed man with a life-expectancy of at least fifteen years.	Weak
Offer early PSA testing to well-informed men at elevated risk of having PCa: • men from 50 years of age; • men from 45 years of age and a family history of PCa; • men of African descent from 45 years of age; • men carrying *breast cancer gene 2 (BRCA2)* mutations from 40 years of age.	Strong
Offer a risk-adapted strategy (based on initial PSA level), with follow-up intervals of two 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 up to eight years in those not at risk.	Weak
Stop early diagnosis of PCa based on life expectancy and performance status; men who have a life-expectancy of < fifteen years are unlikely to benefit.	Strong

5.1.6 Genetic testing for inherited prostate cancer

Increasing evidence supports the implementation of genetic counselling and germline testing in early detection and PCa management [153]. Several commercial screening panels are now available to assess the main PCa risk genes [154]. However, it remains unclear when germline testing should be considered and how this may impact localised and metastatic disease management. Germline *BRCA1* and *BRCA2* mutations occur in approximately 0.2% to 0.3% of the general population [155]. It is important to understand the difference between somatic testing, which is performed on the tumour, and germline testing, which is performed on blood or saliva and identifies inherited mutations. Genetic counselling is required prior to and after undergoing germline testing.

Germline mutations can drive the development of aggressive PCa. Therefore, the consensus is the following men, with a personal or family history of PCa or other cancer types arising from DNA repair gene mutations should be considered for germline testing:

- Men with metastatic PCa who are candidates for targeted treatment;
- Men with BRCA mutations on somatic testing;
- Men with multiple family members diagnosed with csPCa at age < 60 years or a family member who died from PCa;
- Men with a family history of high-risk germline mutations or a family history of multiple cancers on the same side of the family.

Further research in this field (including not so well-known germline mutations) is needed to develop screening, early detection and treatment paradigms for mutation carriers and family members.

*5.1.7 **Guidelines for germline testing****

Recommendations	Strength rating
Consider germline testing in men with multiple family members diagnosed with PCa at age < 60 years or a family member who died from PCa.	Weak
Offer germline testing in men with a family history of high-risk germline mutations or a family history of multiple cancers on the same side of the family.	Strong
Offer germline testing to patients with breast cancer gene (BRCA) mutations on somatic testing	Strong

**Genetic counselling is required prior to germline testing.*

5.2 Diagnostic tools

The different available diagnostic tools can be used separately, or in multiple-tier combinations and/or sequences to indicate prostate biopsy.

*5.2.1 **Digital rectal examination***

In ~18% of cases, PCa is detected by suspect DRE alone, irrespective of PSA level [156]. A suspect DRE in patients with a PSA level ≤ 2 ng/mL has a positive predictive value (PPV) of 5–30% [156]. In the ERSPC trial, an abnormal DRE in conjunction with an elevated PSA more than doubled the risk of a positive biopsy (48.6% vs. 22.4%) [157]. An abnormal DRE is associated with an increased risk of a higher ISUP grade, predicts clinically significant PCa in men under AS (active surveillance) [158] and is an indication for MRI and biopsy [157, 159]. Clinical T-staging is dependent on DRE, and it remains a strong predictor of advanced PCa (OR: 11.12 for cT3 and OR: 5.28 for cT4) [160].

*5.2.2 **Prostate-specific antigen***

Prostate-specific antigen (a glycoprotein enzyme secreted by prostate epithelial cells) is the primary test in the suspicion of PCa. Its use as a serum marker has revolutionised PCa diagnosis [161]. Prostate-specific antigen is organ- but not cancer specific; therefore, it may be elevated in benign prostatic hyperplasia (BPH), prostatitis and other non-malignant conditions. There are no agreed standards for defining PSA thresholds [162]. It is a continuous parameter, with higher levels indicating greater likelihood of PCa. Some men may harbour PCa despite having low serum PSA [163]. Table 5.2 demonstrates the occurrence of any PCa and ISUP ≥ grade 2 PCa in systematic biopsies at low PSA levels, precluding an optimal PSA threshold for detecting non-palpable but csPCa.

Table 5.2: Risk of PCa identified by systemic PCa biopsy in relation to low prostate-specific antigen values [163]

PSA level (ng/mL)	Risk of PCa (%)	Risk of ISUP grade ≥ 2 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

In a screening situation, the most commonly applied threshold for PSA is ≥ 3.0 ng/ml, resulting in 16.5% of invited men returning a positive test [164]. The risk of finding PCa at a specific PSA threshold in a clinical cohort may be different than in a screening situation, due to differences in prevalence, protocol for referral, and diagnostic algorithm. PSA keeps its diagnostic value for cancer detection in symptomatic patients [165]. A review and meta-analysis on the diagnostic accuracy of PSA (≥ 4.0 ng/ml) for the detection of PCa transrectal ultrasound (TRUS) in clinical patients found an estimated combined sensitivity of 0.93 and specificity of 0.20 PSA production is androgen dependent and 5α-reductase inhibitors (e.g. finasteride, dutasteride) used for benign prostatic enlargement of the prostate such as finasteride or dutasteride will reduce PSA levels by 50% [166]. In such cases, PSA level should be corrected before a decision about further investigation is made.

In case of a moderately elevated PSA (up to 10 ng/mL), a repeated test after a few weeks should be considered to confirm the increase before going to continue the diagnostic analysis. Repeat PSA should be performed in the same laboratory using the same assay under standardised conditions (i.e. no ejaculation, manipulations, and urinary tract infections [UTIs]) [167, 168]. The type of PSA assay used may impact PSA values and rates of PSA above certain fixed thresholds [169].

A repeat PSA test before prostate biopsies in men with an initial PSA 3–10 ng/mL reduced the indication for biopsies in 16.8% of men while missing 5.4% ISUP grade > 1 in the Stockholm3 trial [170]. Similarly, in the Prostate Testing for Cancer and Treatment (ProtecT) trial men with a more than 20% lower repeat-PSA analysis within seven weeks had a lower risk of PCa (OR: 0.43, 95% CI: 0.35–0.52) as well as a lower risk of ISUP grade ≥ 2 (OR: 0.29, 95% CI: 0.19–0.44) [171]. A study with a PSA interval of four weeks showed similar findings of a reduced risk of PCa and ISUP grade > 1 [172]. These observations indicate that an early repeat-PSA prior to the decision of prostate biopsies has prognostic information.

*5.2.3 **Prostate-specific antigen density***

Prostate-specific antigen density (PSA-D) is the level of serum PSA divided by the prostate volume. The higher the PSA-D, the more likely it is that the PCa is clinically significant; in particular in smaller prostates when a PSA-D cut-off of 0.15 ng/mL/cc was applied [195]. Several studies found a PSA-D over 0.1–0.15 ng/mL/cc predictive of PCa [173, 174]. Patients with a PSA-D below 0.09 ng/mL/cc were found unlikely (4%) to be diagnosed with csPCa [175]. PSA-D is one of the strongest predictors in risk calculators.

PSA-D remains currently limited due to the lack of standardisation of prostate volume estimation that can be assessed by DRE or by imaging (TRUS or MRI using various techniques such as ellipsoid formula or planimetry). Nonetheless, one study involving seven radiologists who assessed prostate volume on 40 MRI scans using two different ellipsoid methods and a manual planimetry method suggested that intra and inter-reader reproducibility of the three methods were excellent with intraclass correlation coefficient > 0.90 [176]. In a series of 640 men, TRUS found prostate volumes on average 8% smaller than MRI; in the 109 men who underwent RP, MRI-derived prostate volume was better correlated to the volume of the surgical specimen than TRUS-derived volume [177].

Transabdominal ultrasound overestimated the prostate volume by 9.9 ml [178]. Therefore, the use of transabdominal ultrasound to evaluate prostate volume is discouraged.

*5.2.4 **Imaging***

5.2.4.1 Magnetic resonance imaging

Multi-parametric MRI combines T2-weighted, diffusion-weighted, and dynamic contrast-enhanced imaging. Although MRI is mainly initiated after suspicion of PCa based on PSA and/or DRE, it has also been analysed as an initial test [179]. Besides suggesting the presence of PCa, imaging also allows targeted prostate biopsy and provides staging information.

Prostate cancer appears as areas with low signal intensity on T2-weighted imaging, restriction of diffusion and early and intense enhancement on perfusion imaging. However, there is substantial overlap between the appearances of PCa and some prostate benign conditions. The Prostate Imaging-Reporting and Data System (PI-RADS) has been proposed to standardize interpretation and stratify men with suspected PCa on a 1- to 5- risk scale of having csPCa [180, 181].

Correlation with RP specimens shows that MRI has good sensitivity for the detection and localisation of ISUP grade group ≥ 2 cancers, especially when their diameter is larger than 10 mm [182]. MRI is less sensitive in identifying ISUP grade group 1 PCa. It identifies less than 30% of ISUP grade 1 cancers smaller than 0.5 cc identified on RP specimens by histopathology analysis [182-185].

The good sensitivity of magnetic resonance imaging for ISUP grade group ≥ 2 cancer was further confirmed in patients who underwent template biopsies. In a Cochrane meta-analysis which compared MRI to template biopsies (≥ 20 cores) in biopsy-naïve and repeat-biopsy settings, MRI had a pooled sensitivity of 0.91 (95% CI: 0.83–0.95) and a pooled specificity of 0.37 (95% CI: 0.29–0.46) for ISUP grade group > 2 cancers. For ISUP grade ≥ 3 cancers, MRI pooled sensitivity and specificity were 0.95 (95% CI: 0.87–0.99) and 0.35 (95% CI: 0.26–0.46), respectively [186].

In a meta-analysis of seventeen studies involving men with suspected or biopsy-proven PCa, the average PPVs for ISUP grade group ≥ 2 cancers of lesions with a PI-RADS version 2.1 score of 3, 4 and 5 were 16% (7–27%), 59% (39–78%), and 85% (73–94%), respectively, but with significant heterogeneity among studies [187].

In biopsy naïve men, an MRI-based indication for biopsy after referral, leads to lower rates of biopsy, lower rates of men diagnosed with PCa labelled as insignificant, and more men with PCa labelled as csPCa [121, 186, 188-190]. This is also true in men with prior negative biopsy [186, 191] (see section 5.4.2).

5.2.4.2 Transrectal ultrasound and ultrasound-based techniques

Standard TRUS is not reliable at detecting PCa [192] and the diagnostic yield of additional biopsies performed on hypoechoic lesions is negligible [190]. New sonographic modalities such as micro-Doppler, sonoelastography or contrast-enhanced US provided promising preliminary findings, either alone, or combined into the so-called 'multi-parametric US' [193, 194]. In the multi-parametric US vs. multi-parametric MRI to diagnose PCa (CADMUS) trial, 306 patients underwent both multi-parametric MRI and multi-parametric US composed of B-mode, Colour Doppler, real-time elastography, and contrast-enhanced US. Patients with at least one positive test underwent targeted biopsy. Multi-parametric US detected 4.3% fewer csPCa while submitting 11.1% more patients to biopsy than MRI [195].

High-resolution micro-US shows improved spatial resolution but struggles to assess the anterior part of large prostates. Two prospective trials assessed MRI and micro-US interpreted in a blinded manner before combined targeted and systematic biopsy. In one, MRI and micro-US detected respectively 60 (76%) and 58 (73%) of the 79 csPCas, while systematic sampling detected 45/79 cases (57%). MRI-targeted biopsy detected seven csPCas missed by micro-US; of these three were anterior lesions. Micro-US-guided biopsy detected five csPCas missed by MRI; of these, three were at the apex [196]. In the other study, MRI- and micro-US-targeted biopsy depicted csPCa in 37 (39%) and 33 (35%) of the 94 men, respectively while the MRI- plus micro-US-targeted pathway detected 38 csPCa [197]. These findings suggest that MRI and micro-US could complement each other. Micro-US could also be an interesting alternative to MRI/fusion since biopsy operators who are aware of MRI findings can localise most MRI lesions on micro-US and, thus, target them with direct US image guidance [198]. Of note, evaluation of micro-US inter-operator variability is currently lacking.

5.2.4.3 Prostate-specific antigen-Positron emission tomography/Computed tomography (or Magnetic resonance imaging)

Though mainly used for staging purposes, PSMA-PET/CT (or -PET/MRI) prostate expression may be used to indicate and target biopsies. For csPCa detection, a pooled sensitivity of 0.89 and a pooled specificity of 0.56 have been reported [199]. In a prospective trial of 291 patients, combined PSMA + MRI improved negative predicted value (NPV) compared with MRI alone (91% vs. 72%, test ratio = 1.27 [1.11–1.39], $p < 0.001$). Sensitivity also improved (97% vs. 83%, $p < 0.001$), but specificity was reduced (40% vs. 53%, $p = 0.011$) [122].

*5.2.5 **Blood and urine biomarkers***

Urine and serum biomarkers as well as tissue-based biomarkers have been proposed for improving detection and risk stratification of PCa patients, potentially avoiding unnecessary biopsies. However, further studies are necessary to validate their efficacy [200].

5.2.5.1 Blood based biomarkers: PHI/4K score/IsoPSA/Stockholm3/Proclarix

The use of biomarkers (included in a nomogram) may help in predicting indolent PCa [201, 202]. Several assays measuring a panel of kallikreins in serum or plasma are now commercially available, including the U.S. Food and Drug Administration (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] in addition to other parameters age, DRE and prior biopsy status). Both tests are intended to reduce the number of unnecessary prostate biopsies in PSA-tested men. A few prospective multi-centre studies demonstrated that both the PHI and 4K score test out-performed f/t PSA PCa detection, with an improved prediction of csPCa in men with a PSA between 2–10 ng/mL [203, 204]. In a head-to-head comparison both tests performed equally [205].

In contrast to the 4K score and PHI, which focus on the concentration of PSA isoforms, IsoPSA utilises a technology which focuses on the structure of PSA. In a multi-centre prospective validation in 271 men the assay area under curve (AUC) was 0.784 for high-grade vs. low-grade cancer/benign histology, which was superior to the AUCs of total PSA and percent free PSA [208]. In men with a negative mpMRI, PSA-D, 4K score and family history predicted the risk of csPCa on biopsy and using a nomogram reduced the number of negative biopsies and indolent cancers by 47% and 15%, respectively, while missing 10% of csPCa [206].

The Stockholm3 test is a prediction model that is based on several clinical variables (age, first-degree family history of PCa, and previous biopsy), blood biomarkers (total PSA, free PSA, ratio of free PSA to total PSA, human kallikrein 2, macrophage inhibitory cytokine-1, and *microseminoprotein*-β *[MSMB])*, and a polygenic risk score for predicting the risk of PCa with ISUP grade group ≥ 2, and was shown to reduce the percent of clinically insignificant cancers when used in combination with MRI in a PSA screening population [207]. It also has the potential to decrease the number of mpMRI scans required in prostate cancer screening [208].

The Proclarix® test is a blood-based test that estimates the likelihood of csPCa according to measurement results for thrombospondin-1, cathepsin D, total PSA, percentage free PSA and patient age. This test has been correlated with the detection of significant PCa, notably in case of equivocal MRI (PI-RADS 3 lesions) [209].

5.2.5.2 Urine biomarkers: PCA3/SelectMDX/Mi Prostate score (MiPS)/ExoDX

Prostate cancer gene 3 (PCA3) is an overexpressed long non-coding RNA (lncRNA) biomarker that is detectable in urine sediments obtained after three strokes of prostatic massage during DRE. However, the clinical utility of the commercially available Progensa urine test for PCA3 for biopsy decision-making remains uncertain. Still, combining MRI findings with the PCA3 score may improve risk stratification [210].

The SelectMDX test is similarly based on mRNA biomarker isolation from urine. The presence of HOXC6 and DLX1 mRNA levels is assessed to provide an estimate of the risk of both presence of PCa on biopsy as well as presence of high-risk cancer [211]. A multi-centre trial evaluated SelectMDX in men with an MRI PI-RADS score < 4 or PI-RADS score < 3, and the percentage of missed csPCas was 6.5% and 3.2%, respectively, whereas 45.8% and 40% of biopsies were avoided [212]. Hendriks *et al.*, found more biopsies were avoided and more high-grade PCas detected in an MRI-based biopsy strategy compared to a SelectMDX strategy. When both tests were combined, more Gleason grade > 1 lesions were found, but the number of negative or low-grade cancer biopsies more than doubled [202]. Combining SelectMDX and MRI in men with a PSA between 3–10 ng/mL had a negative predictive value (NPV) of 93% [213]. The clinically added value of SelectMDX in the era of upfront MRI and targeted biopsies remains unclear [214].

TMPRSS2-ERG fusion, a fusion of the trans-membrane protease serine 2 (TMPRSS2) and the ERG gene can be detected in 50% of PCas [215]. When detection of TMPRSS2-ERG in urine was added to PCA3 expression and serum PSA (Mi(chigan)Prostate Score [MiPS]), cancer prediction improved [216]. Exosomes secreted by cancer cells may contain mRNA diagnostic for high-grade PCa [217, 218]. Use of the ExoDx Prostate IntelliScore urine exosome assay resulted in avoiding 27% of unnecessary biopsies when compared to standard of care (SOC). However, currently, both the MiPS-score and ExoDx assay are considered investigational.

In the screening population of the ERSPC study the use of both PCA3 and 4K panel when added to the risk calculator led to an improvement in AUC of less than 0.03 [219]. Based on the available evidence, some biomarkers could help in discriminating between aggressive and non-aggressive tumours with an additional value compared to the prognostic parameters currently used by clinicians [220]. However, upfront MRI is also likely to affect the utility of above-mentioned biomarkers (see Section 5.2.3.2).

*5.2.6 **Guidelines for screening and individual early detection***

Recommendations	**Strength rating**
In asymptomatic men with a prostate-specific antigen (PSA) level between 3 and 10 ng/mL and a normal digital rectal examination (DRE), repeat the PSA test prior to further investigations.	Weak
In asymptomatic men with a PSA level between 3 and ps. Go20 ng/mL and a normal DRE, use one of the following tools for biopsy indication: • risk-calculator, provided it is correctly calibrated to the population prevalence; • magnetic resonance imaging of the prostate.	Strong
• an additional serum, urine biomarker test	Weak

5.3 *Pathology of prostate needle biopsies*

5.3.1 Processing

Prostate core biopsies from different sites are processed separately, as delivered by the biopsy operator. Before processing, the number and length of the cores are recorded. The length of biopsy tissue significantly correlates with the PCa detection rate [221]. In case individual cores can clearly be identified in submitted jars, a maximum of three cores should be embedded per tissue cassette, and sponges or paper should be used to keep the cores stretched and flat to achieve optimal flattening and alignment [222, 223]. To optimise detection of small lesions and improve accuracy of grading, paraffin blocks should be cut at three levels and intervening unstained sections may be kept for immunohistochemistry (IHC) [224].

5.3.2 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 [224]. Diagnostic uncertainty is resolved by intradepartmental or external consultation [224]. Sections 5.3.2.1 and 5.3.2.2 list the recommended terminology and item list for reporting prostate biopsies [223]. Type and subtype of PCa should be reported such as for instance acinar adenocarcinoma, ductal adenocarcinoma and small or large cell neuroendocrine carcinoma, even if representing a small proportion of the PCa. The distinct aggressive nature of small/large cell neuroendocrine carcinoma should be commented upon in the pathology report [223]. Apart from grading acinar and ductal adenocarcinoma, the percentage of Gleason grade 4 component should be reported in Gleason score 7 (3+4 and 4+3) PCa biopsies. Percentage Gleason grade 4 has additional prognostic value and is considered in some AS protocols [225, 226]. Considerable evidence has been accumulated in recent years supporting that among the Gleason grade 4 patterns, cribriform pattern carries an increased risk of biochemical recurrence, metastatic disease and death of disease [227, 228]. Reporting of this sub-pattern based on established criteria is recommended [101, 229]. Intraductal carcinoma, defined as an extension of cancer cells into pre-existing prostatic ducts and acini, distending them, with preservation of basal cells [101], should be distinguished from high-grade prostatic intraepithelial neoplasia (PIN) [230] as it conveys unfavourable prognosis in terms of biochemical recurrence and cancer-specific survival (CSS) [231, 232]. Its presence should be reported whether occurring in isolation or associated with adenocarcinoma [101]. Some intra-epithelial lesions have architectural complexity and/or cytological atypia exceeding those of high-grade PIN but fall short for a definitive diagnosis of IDC. These lesions have been referred to as Atypical Intraductal Proliferation (AIP) and amongst others encompass lesions that were previously classified as cribriform high-grade PIN. Small retrospective series suggest that AIP at biopsy is associated with unsampled IDC [233, 234]. Therefore, presence of AIP should be reported and commented on in non-malignant biopsies and biopsies with ISUP grade group 1 and 2 cancers in the absence of overt invasive cribriform and IDC.

5.3.2.1 Recommended terminology for reporting prostate biopsies [235]

Heading
Benign/negative for malignancy; if appropriate, include a description
Active inflammation
Granulomatous inflammation
High-grade prostatic intraepithelial neoplasia (PIN)
High-grade PIN with atypical glands, suspicious for adenocarcinoma
Focus of atypical glands/lesion suspicious for adenocarcinoma/atypical small acinar proliferation, suspicious for cancer
Adenocarcinoma, provide type and subtype, and presence or absence of cribriform pattern
Atypical intraductal proliferation (AIP)
Intraductal carcinoma

Each biopsy site should be reported individually, including its location (in accordance with the sampling site) and histopathological findings, which include the histological type and the ISUP 2019 grade group [101, 236, 237]. For MRI targeted biopsies consisting of multiple cores per target the aggregated (or composite) ISUP grade group should be reported per targeted lesion [101]. If the targeted biopsies are negative, presence of specific benign pathology should be mentioned, such as dense inflammation, fibromuscular hyperplasia or granulomatous inflammation [101, 238]. A global ISUP grade group comprising all systematic (non-targeted) and targeted biopsies is also reported (see Section 4.2). The global ISUP grade group takes into account all biopsies positive

for carcinoma, by estimating the total extent of each Gleason grade present. For instance, if three biopsy sites are entirely composed of Gleason grade 3 and one biopsy site of Gleason grade 4 only, the global ISUP grade group would be 2 (i.e. GS 7[3+4]) or 3 (i.e. GS 7[4+3]), dependent on whether the extent of Gleason grade 3 exceeds that of Gleason grade 4, whereas the worst grade would be ISUP grade group 4 (i.e. GS 8[4+4]). Neither global nor worst ISUP grade group is clearly superior over the other [239]. The majority of clinical studies have not specified whether global or worst biopsy grade was taken into account. In addition to GS /ISUP grade group, the presence/absence of intraductal/invasive cribriform pattern should be reported [101, 236, 237]. Furthermore, in biopsy GS 7 (ISUP grade group 2 and 3) percentage Gleason grade 4 should be monitored at the case and/or biopsy level [101, 237]. Lymphovascular invasion (LVI), EPE and ejaculatory duct/seminal vesicle involvement must each be reported, if identified, since they carry unfavourable prognostic information [240, 241].

Recently, a series of studies have demonstrated that computer-assisted PCa grading artificial intelligence algorithms can perform grading at the level of experienced genito-urinary pathologists. These algorithms have potential in supporting grading of less experienced pathologists, by reducing inter-observer variability, and in quantitative analyses. However, more extensive and prospective validation of these algorithms is needed for implementation in daily clinical practise [101, 236, 237, 242]. The proportion of systematic (non-targeted) carcinoma-positive cores as well as the extent of tumour involvement per biopsy core correlate with the ISUP grade group, tumour volume, surgical margins and pathological stage in RP specimens and predict BCR, post-prostatectomy progression and RT failure. These parameters are included in nomograms created to predict pathological stage and SV invasion after RP and RT failure [243, 244]. A pathology report should therefore provide both the number 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 [245]. An extent of >50% of adenocarcinoma in a single core is used as a cut-off in some AS protocols [246] triggering immediate treatment vs. AS in patients with ISUP grade group 1 (see Section 6.1.1.1).

5.3.2.2 Recommended item list for reporting prostate cancer biopsies [101, 236, 237]

Type of carcinoma
Primary and secondary Gleason grade, per biopsy site and global International Society of Urological Pathology (ISUP) grade group
Percentage of global Gleason grade 4 in Gleason Score (GS) 7 biopsies
Presence/absence of intraductal/invasive cribriform carcinoma
Presence of Atypical Intraductal Proliferation (AIP) in intraductal/invasive cribriform-negative cases
Number of cancer-positive biopsy cores
Extent of cancer (in mm or percentage)
For Magnetic resonance imaging (MRI)-targeted biopsies with multiple cores aggregate (or composite) ISUP grade group per lesion For carcinoma-negative MRI-targeted biopsy, specific benign pathology, e.g. fibromuscular hyperplasia or granulomatous inflammation
If present, lymphovascular invasion (LVI), extraprostatic extension and ejaculatory duct/seminal vesicle involvement

*5.3.3 **Tissue-based prognostic biomarker testing***

After a comprehensive literature review and several panel discussions an American Society of Clinical Oncology (ASCO)-EAU-American Urological Association (AUA) multi-disciplinary expert panel made recommendations regarding the use of tissue-based PCa biomarkers. The recommendations were limited to five commercially available tests (Oncotype Dx, Prolaris, Decipher, Decipher PORTOS and ProMark) with extensive validation in large retrospective studies and evidence that their test results might actually impact clinical decision-taking. The selected commercially available tests significantly improved the prognostic accuracy of clinical multi-variable models for identifying men who would benefit of AS and those with csPCa requiring curative treatment, as well as for guidance of patient management after RP. Few studies showed that tissue biomarker tests and MRI findings independently improved the detection of csPCa in an AS setting, but it remains unclear which men would benefit of both tests. Decipher® test outcome has been associated with presence of intraductal/invasive cribriform carcinoma but retains independent value in multi-variable analysis. Since the long-term impact of the use of these commercially available tests on oncological outcome remains unproven and prospective trials are largely lacking, the Panel concluded that these tests should not be offered routinely but only in subsets of patients where the test result provides clinically actionable information, such as for instance in men with favourable intermediate-risk PCa who might opt for AS or men with unfavourable intermediate-risk PCa

scheduled for RT to decide on treatment intensification with hormone therapy (HT) [247].

5.3.4 Tissue samples for homologous recombination repair (HRR)-testing

Homologous recombination repair-testing in the PROfound trial was conducted on archival or recent biopsy tissue from primary or metastatic disease with successful sequencing in 69% [248]. Alterations in HRR genes are relatively unchanged comparing matched treatment-naïve diagnostic and mCRPC biopsies [249, 250]. Whereas there is no preference for use of archival or new metastatic biopsies for HRR-testing, bone biopsies might be associated with lower success rates related to decalcification of tissue [251]. Testing of circulating tumour DNA might be a good alternative if tumour tissue is not available [250, 252]. With tissue as reference, ctDNA showed 81% positive and 92% negative percentage agreement [253].

5.3.5 Histopathology of radical prostatectomy specimens

5.3.5.1 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, multi-focality 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 with this method missed 5% of positive margins and 7% of EPE [254].

The entire RP specimen should be inked 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. 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 [99]. 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.

5.3.5.2 Radical prostatectomy specimen report

The pathology report provides essential information on the prognostic characteristics relevant for clinical decision-making (Table 5.6). As a result of the complex information to be provided for each RP specimen, the use of synoptic(-like) or checklist reporting is recommended. Synoptic reporting results in more transparent and complete pathology reporting [255].

Table 5.3: Mandatory elements provided by the pathology report

Histopathological (sub)type
Type of carcinoma, e.g., conventional acinar adenocarcinoma, (small cell) neuroendocrine cell carcinoma or ductal carcinoma
Subtype and unusual variants, e.g. pleomorphic giant cell or mucinous
Histological grade
Primary (predominant) Gleason grade Secondary Gleason grade Tertiary Gleason grade (if applicable) Global ISUP 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: • indicate whether it is focal or extensive (see Section 5.2.9.4.4); • specify sites; • indicate whether there is seminal vesicle invasion. *If applicable, regional lymph nodes:* • location; • number of nodes retrieved; • number of nodes involved.
Surgical margins
If carcinoma is present at the margin: • specify sites; • extent: focal or extensive (see Section 5.2.9.4.6) • (highest) grade at margin.
Other
Presence of lymphovascular/angio-invasion Location of dominant tumour Presence of intraductal carcinoma/cribriform architecture

5.3.5.3 ISUP grade group in prostatectomy specimens

Grading of conventional prostatic adenocarcinoma using the Gleason system is the strongest prognostic factor for clinical behaviour and treatment response [100]. The GS is incorporated in nomograms that predict disease-specific survival (DSS) after prostatectomy [256, 257]. The ISUP grade group in prostatectomy specimens is determined mostly in a similar way as in biopsies, with a minor exception, i.e. the exclusion of minor (< 5%) high-grade components from the ISUP grade group. For instance, in a carcinoma almost entirely composed of Gleason grade 3 the presence of a minor (< 5%) Gleason grade 4 or 5 component is not included in the GS (ISUP grade group 1), but its presence is commented upon [101]. In case of multi-focality the ISUP grade group of the index lesion i.e. the tumour having the highest grade, stage or volume, is given.

5.3.5.4 Definition of extra-prostatic extension

Extra-prostatic extension is defined as carcinoma mixed with peri-prostatic adipose tissue, or tissue that extends beyond the prostate gland boundaries (e.g., neurovascular bundle, anterior prostate). Microscopic bladder neck invasion is considered EPE. It is useful to report the location and extent of EPE because the latter is related to recurrence risk [258]. There are no internationally accepted definitions of focal or microscopic, vs. non-focal or extensive EPE. Some describe focal as a few glands [259] or <1 high-power field in one or at most two sections whereas others measure the depth of extent in millimetres [259]. At the apex of the prostate, tumour mixed with skeletal muscle does not constitute EPE. In the bladder neck, microscopic invasion of smooth muscle fibres is not equated to bladder wall invasion, i.e. not as pT4, because it does not carry independent prognostic significance for PCa recurrence and should be recorded as EPE (pT3a) [260, 261]. Stage pT4 is assigned when the tumour invades the bladder muscle wall as determined macroscopically [94].

5.3.5.5 PCa volume

Although PCa volume at RP correlates with tumour grade, stage and surgical margin status, the independent prognostic value of PCa volume has not been established [259, 262, 263]. Improvement in prostatic radio-imaging allows more accurate pre-operative measurement of cancer volume. Since the independent value of pathological tumour volume at RP has not been established, reporting of the diameter/volume of the dominant tumour nodule, or a rough estimate of the percentage of cancer tissue, is optional [264].

5.3.5.6 Surgical margin status

Surgical margin status 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 [265] 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 [266]. Surgical margin is separate from pathological stage, and a positive margin is not evidence of EPE [267]. There is evidence for a relationship between margin extent and recurrence risk [268, 269]. Some indication must be given of the multi-focality and extent of margin positivity, such as the linear extent in mm of involvement: focal, ≤ 1 mm vs. extensive, > 1 mm [270], or number of blocks with positive margin involvement. Gleason score at the positive margin was found to correlate independently with outcome and should be reported [255, 268, 271].

5.3.5.7 *Intra-operative assessment of surgical margin status*

Intra-operative surgical margin assessment can be performed during RP to reduce positive margins and increase neurovascular bundle preservation. A SR reported a 1-15% decrease of positive surgical margins in eight out of ten studies [272]. Intra-operative evaluation of the posterolateral prostatic margin according to the neurovascular structure-adjacent frozen section examination (NeuroSAFE) technique is a systematic way of intra-operative surgical margin evaluation [273]. Non-randomised studies showed that men subjected to NeuroSAFE had lower positive surgical margin rates and more frequently underwent uni- or bilateral nerve-sparing surgery [273-276]. Pending the results on long-term oncological and functional outcome as well as the outcome of the randomised NeuroSAFE PROOF trial, intra-operative frozen section analysis should not be considered standard of care [277].

5.4 Biopsy indication

5.4.1 ***Risk assessment before MRI and biopsy***

An elevated risk of significant PCa is established based on one or more of the primary diagnostic tools applied, such as PSA level, DRE, or primary imaging. While in the classic diagnostic algorithm the indication for biopsy was generally solely based on a PSA-threshold or abnormal DRE, different two- or three-tier sequential / conditional pathways are now available to indicate prostate biopsy, such as imaging and/or biomarkers. These can be combined and/or sequenced into two or multiple-tier conditional diagnostic pathways (e.g. PSA -> MRI, PSA -> risk calculator, PSA -> risk calculator -> MRI, etc). Age, co-morbidity, life expectancy, and therapeutic consequences should also be considered and discussed beforehand [278].

The chosen diagnostic algorithm may be elected based on availability, expertise, and resources. The different approaches impact cancer detection rates, number of (un)necessary biopsies, number of patient visits, and option of targeted biopsies. The elected strategy may also be decided based on prevalence of disease in men entering the pathway (e.g. screening versus clinical symptoms).

Different sequences and combinations of these tools, lead to different rates of biopsy indications, detection rates of insignificant PCa, and significant PCa, but also on the burden and costs of the diagnostic algorithm [279].

5.4.1.1 *Risk calculators assessing the risk of csPCa*

At different steps during the diagnostic process, available parameters may be combined into risk calculators to optimise risk-assessment of csPCa. Validation and adaption to the target population are important issues before use. Risk calculators, combining clinical data (age, DRE findings, PSA level, prostate volume, etc.) may be useful in helping to determine (on an individual basis) what the potential risk of cancer may be, thereby improving the balance of the cancer detection rates and number of biopsies [280].

Several tools developed from cohort studies are available including (among others) the calculator derived from the ERSPC cohort (http://www.prostatecancer-riskcalculator.com/seven-prostate-cancer-risk-calculators) that has been updated by incorporating the 2014 ISUP Pathology Gleason Grading and Cribriform growth [150], and the one derived from the Prostate Cancer Prevention Trial (PCPT) cohort (PCPTRC 2.0 https://riskcalc.org/PCPTRC/). However, calculators are limited by their dependency on disease prevalence. All calculators show miscalibration when tested in populations with a different prevalence than that of the training population of the model. Recalibrations taking into account the local prevalence are possible, but this approach is difficult in routine as the local prevalence is difficult to estimate and may change over time.

5.4.1.2 *Using risk-stratification to avoid Magnetic resonance imaging scans and biopsy procedures*

A retrospective analysis including 200 men from a prospective database of patients who underwent MRI and combined systematic and targeted biopsy showed that upfront use of the Rotterdam Prostate Cancer Risk Calculator would have avoided MRI and biopsy in 73 men (37%). Of these 73 men, ten had ISUP grade group 1 cancer and 4 had ISUP grade group ≥ 2 cancer [281]. A prospective multi-centre study evaluated several diagnostic pathways in 545 biopsy-naive men who underwent MRI and systematic and targeted biopsy. Using a PHI threshold of > 30 to perform MRI and biopsy would have avoided MRI and biopsy in 25% of men at the cost of missing 8% of the ISUP grade group ≥ 2 cancers [282]. Another prospective multi-centre trial including 532 men (with or without history of prostate biopsy) showed that using a threshold of ≥ 10% for the Stockholm3 test to perform MRI and biopsy would have avoided MRI and biopsy in 38% of men at the cost of missing 8% of ISUP grade group ≥ 2 cancers [207]. Finally, a risk calculator developed on 1,486 men who underwent MRI and biopsy was externally validated on a cohort of 946 men from two institutions; using a risk threshold that provided 95% sensitivity in the development cohort could have avoided 22% of the MRI scans in the validation cohort while missing 5% of csPCa [283].

5.4.2 *MRI based indication for biopsy*

5.4.2.1 *MRI as a triage test for biopsy ('MRI pathway')*

Owing to its high sensitivity, MRI showed an excellent NPV for ruling out the presence of csPCa not only at subsequent biopsy [284], but also after four years of follow-up [285].

The diagnostic yield and number of biopsy procedures potentially avoided by the 'MR pathway' (in which only patients with positive MRI undergo biopsy) depends on the Likert/PI-RADS threshold used to define a positive MRI. In pooled studies on biopsy-naive patients and patients with prior negative biopsies, a Likert/PI-RADS threshold of ≥ 3 would have avoided 30% (95% CI: 23–38) of all biopsy procedures while missing 11% (95% CI: 6–18) of all detected ISUP grade group ≥ 2 cancers (relative percentage) [186]. Increasing the threshold to ≥ 4 would have avoided 59% (95% CI: 43–78) of all biopsy procedures while missing 28% (95% CI: 14–48) of all detected ISUP grade group ≥ 2 cancers [186]. Of note, the percentages of negative MRI (Likert/PI-RADS score ≤ 2) may show substantial variability among series. In the PRECISION, MRI-FIRST and 4M trials were 21.1%, 28.9% and 49%, with related ISUP grade group ≥ 2 cancer prevalence of 27.7% (23.7–32.6), 37.5% (31.4–43.8), and 30% (ND) respectively [121, 189, 190].

In the MR PROPER trial, a prospective, multi-centre, non-randomised opportunistic early detection setting (PSA > 3 ng/mL), comparable rates of ISUP grade group ≥ 2 cancer detection (24% vs. 25%) were obtained by the MRI pathway and by a strategy indicating systematic biopsy based on a risk calculator. However, the MRI pathway avoided biopsy in more men as compared to the diagnostic pathway using a risk calculator (559/1015, 55% vs. 403/950, 42%; difference -13%, 95% 27 CI: -17% to -8.3%; p < 0.01); it also detected less ISUP grade group 1 cancers (84/1015, 8.3% vs. 121/950, 13%; difference 4.5%, 95% CI: 1.8–7.2%; p < 0.01) [286].

5.4.2.2 *Combining MRI and PSA Density*

Prostate-specific antigen density (PSA-D) may help refine the risk of csPCa in patients undergoing MRI as PSA-D and the PI-RADS score are significant independent predictors of csPCa at biopsy [287, 288]. Combinations of PSA-D and MRI have been explored [289, 290], showing guidance in biopsy-decisions whilst safely avoiding redundant biopsy testing and detection of insignificant PCa. In a meta-analysis of eight studies, pooled MRI NPV for ISUP grade group ≥ 2 cancer was 84% (95% CI: 81–87) in the whole cohort, 83% (95% CI: 80–84) in biopsy-naive men and 88% (95% CI: 85–91) in men with prior negative biopsies. In the subgroup of patients with PSA-D < 0.15 ng/mL/cc, NPV increased to respectively 90% (95% CI: 87–93), 89% (95% CI: 83–93) and 94% (95% CI: 91–97) [291]. In contrast, the risk of ISUP grade group ≥ 2 cancer is as high as 27–40% in patients with negative MRI and PSA-D > 0.15–0.20 ng/mL/cc [189, 288, 292-294].

Based on a meta-analysis of > 3,000 biopsy-naive men, a risk-adapted data table of csPCa was developed, linking PI-RADS score (1-2, 3, and 4-5) to PSA-D categories (< 0.10, 0.10–0.15, 0.15–0.20 and > 0.20 ng/mL) (Table 5.4) [289]. This risk-adapted matrix table may guide the decision to perform a biopsy.

In a multi-centre retrospective cohort of 1476 men with PIRADS 3 lesions and a prevalence of 18.5% of ISUP grade group ≥ 2 cancer, age, prior negative biopsy and PSA-D were significant independent predictors of the presence of ISUP grade group ≥ 2 cancer at subsequent systematic and targeted biopsy. Applying a PSA-D cut-off of 0.15 ng/mL/cc, 817 biopsy procedures (58.4%) would have been avoided at the cost of missing ISUP grade group ≥ 2 cancer in 91 men (6.5%); ISUP grade group 1 cancer would not have been detected in 115 men (8.2%) [295]. Two studies provided follow-up data for patients with PI-RADS scores of 1-3 and PSA-D <0.15 ng/ml/cc for whom biopsy was omitted. The cumulative incidence of ISUP grade group ≥ 2 cancer detection was 1.3% at two years [296] and 3.2% at 36 months [297].

Table 5.4: Risk data table of clinically significant prostate cancer, related to PI-RADS score and PSA-D categories in biopsy-naive men, clinically suspected of having significant disease [289]*

Detection of clinically significant prostate cancer (ISUP grade 2 and higher)					
		PSA-density risk groups			
PI-RADS risk categories	Prevalence ISUP ≥ 2 PCa	Low < 0.10	Intermediate-low 0.10–015	Intermediate-high 0.15–0.20	High ≥ 0.20
		31% (678/2199)	28% (612/2199)	16% (360/2199)	25% (553/2199)
Compiled totals of csPCa risk					
PI-RADS 1–2	6% (48/839)	3% (11/411)	7% (17/256)	8% (8/104)	18% (12/68)

PI-RADS 3	16% (41/254)	4% (3/74)	13% (11/88)	29% (12/41)	29% (15/51)
PI-RADS 4–5	62% (687/1106)	31% (59/189)	54% (144/286)	69% (148/215)	77% (336/434)
All PI-RADS	35% (776/2199)	11% (73/674)	28% (172/612)	47% (168/360)	66% (363/553)
Risk-adapted matrix table for biopsy decision management					
PI-RADS 1–2		No biopsy	No biopsy	No biopsy	Consider biopsy
PI-RADS 3		No biopsy	Consider biopsy	Highly consider biopsy	Perform biopsy
PI-RADS 4–5		Perform biopsy	Perform biopsy	Perform biopsy	Perform biopsy

very low	0–5% csPCa (below population risk) #
low	5–10% csPCa (acceptable risk) ##
Intermediate-low	10–20% csPCa
Intermediate-high	20–30% csPCa
High	30–40% csPCa
Very high	> 40% csPCa

Thompson IM *et al.* N Engl J Med. 2004 May 27;350(22):2239-46. Prevalence of prostate cancer among men with a prostate-specific antigen level < or = 4.0 ng/mL. [163].

Table adapted from: Schoots, IG and Padhani AR. BJU Int 2021 127(2):175. Risk-adapted biopsy decision based on prostate magnetic resonance imaging and prostate-specific antigen density for enhanced biopsy avoidance in first prostate cancer diagnostic evaluation, with permission from Wiley.

5.4.2.3 Risk calculators incorporating MRI finding

Several groups have developed comprehensive risk calculators which combine MRI findings with simple clinical data as a tool to predict subsequent biopsy results [298]. Some calculators underwent external validation with good results both in terms of discrimination and clinical utility and tended to outperform risk calculators not incorporating MRI findings [299-302]. However, their use is hindered by their miscalibration due to prevalence dependency (see section 5.4.1.1).

5.4.2.4 MRI in screening protocols

The inclusion of MRI may improve the diagnostic algorithm after a screening PSA, as it reduces the number of men that undergo biopsies while detecting more high-grade and less low-grade PCa [179, 303, 304]. The Stockholm-3 (STHLM3) screening trial randomised men with a PSA > 3 ng/mL between standard biopsies (10–12 cores) or MRI and standard plus targeted biopsies in the presence of a suspicious MRI. The percentage of men that underwent prostate biopsies in the standard group was double that of the MRI group. In this non-inferiority trial, the intention-to-treat (ITT) analysis found 18% and 21% ISUP grade group ≥2 cancer and 12% and 4% ISUP grade group 1 cancer in the standard and the MRI group, respectively [304].

In the GÖTEBORG-2 screening trial, 37,887 men between 50 and 60 years of age were invited to undergo regular PSA screening [305]. Participants with a PSA level above 3 ng/mL were randomly allocated to MRI and combined systematic- and targeted biopsy (reference group) or to MRI and targeted biopsy only in case of PI-RADS ≥ 3 lesions (experimental group). In the experimental group, the detection rate of ISUP grade group 1 cancers was reduced by half (detection ratio: 0.46, 95% CI: 0.33–0.64, p < 0.001); that of ISUP grade group ≥ 2 cancers was lower but not significantly different (detection ratio: 0.81, 95% CI: 0.60 to 1.1). In the reference group, ten of the 68 men with ISUP grade group ≥ 2 cancer were diagnosed by systematic biopsy only. All these ten patients were of intermediate risk. Thus, in a screening setting, the 'MRI pathway' may reduce the risk of over-diagnosis by half, at the cost of delaying detection of intermediate-risk tumours in a small percentage of patients. However, these good results were obtained at a single academic centre with double reading of the MRI, which may limit their generalisability in less experienced centres (see Sections 5.5.4).

The IP1-PROSTAGRAM study (PSA > 3 ng/mL; MRI PIRADS [Prostate Imaging – Reporting and Data System] > 2), tested MRI as the initial screening test, showed highest detection of csPCa for MRI compared to a PSA threshold followed by transrectal ultrasound-guided prostate (TRUS) biopsy in a population screening setting, with similar rates of biopsy and insignificant cancer [179]. This study proposed a pathway that combines PSA >=1 ng/ml and MRI score >=4, maintaining the detection of grade group ≥2 cancers while recommending fewer men for biopsies, as the preferred strategy to evaluate in future studies at the first screening round [306].

5.5 Biopsy strategy

Prostate biopsy can be performed using different strategies (systematic, targeted etc) and approaches (i.e. transperineal vs. transrectal).

*5.5.1 **Systematic biopsy strategy***

For systematic biopsies, where no prior imaging is used for targeting, the sample sites should be bilateral from apex to base, as far posterior and lateral as possible in the peripheral gland regardless of the approach used. A 2006 SR showed that twelve is the minimum number of cores for systematic biopsies, with > twelve cores not increasing cancer detection rate significantly [307].

*5.5.2 **Targeted biopsy strategy***

Where MRI has shown a suspicious lesion, MR-targeted biopsy can be obtained through cognitive guidance, US/MR fusion software or direct in-bore guidance. Current literature, including SRs and meta-analyses, does not show a clear superiority of one image-guided technique over another [308-310]. The Target Biopsy Techniques Based on Magnetic Resonance Imaging in the Diagnosis of Prostate Cancer in Patients with Prior Negative Biopsies (FUTURE) randomised trial compared three techniques (cognitive fusion, software fusion, in-bore MRI) of MRI-targeted biopsy in the repeat-biopsy setting and found no differences in cancer detection [309].

*5.5.3 **Targeted biopsy versus systematic biopsy***

5.5.3.1 Increased detection of cancers labelled as clinically significant

The PRECISION (Prostate Evaluation for Clinically Important Disease: Sampling Using Image Guidance or Not?) [121] and PRECISE (Prostate Evaluation for Clinically Important Disease: MRI vs. Standard Evaluation Procedures) [188] prospective trials randomized biopsy naïve patients to either ten to twelve core systematic biopsy or to MRI with subsequent MRI-targeted biopsy (up to four cores) in case of positive MRI. They found that MRI-targeted biopsy significantly out-performed [121] or was not inferior to [188] systematic biopsy for the detection of ISUP grade group ≥ 2 cancers. In pooled data of 25 reports on agreement analysis (head-to-head comparisons) between systematic biopsy (median number of cores: 8–15) and MRI-targeted biopsies (median number of cores: 2–7), the detection ratio (i.e. the ratio of the detection rates obtained by MRI-targeted biopsy alone and by systematic biopsy alone) was 1.12 (95% CI: 1.02–1.23) for ISUP grade group ≥ 2 cancers and 1.20 (95% CI: 1.06–1.36) for ISUP grade group ≥ 3 cancers, and therefore in favour of MRI-targeted biopsy [168]. Another meta-analysis of studies limited to biopsy-naive patients with a positive MRI also found that MRI-targeted biopsy detected significantly more ISUP grade group ≥ 2 cancers than systematic biopsy (risk difference, -0.11 [95% CI: -0.2 to 0.0]; p = 0.05) [311]. This data was confirmed in prospective multi-centre trials evaluated MRI-targeted biopsy in biopsy-naive patients [121, 189].

In a subgroup of 152 patients from the FUTURE trial who underwent both MRI-targeted biopsy and systematic biopsy in a repeat biopsy setting, MRI-targeted biopsy detected significantly more ISUP grade group ≥ 2 cancers than systematic biopsy (34% vs. 16%; p < 0.001, detection ratio of 2.1) [191]. These findings support that MRI-targeted biopsy significantly out-performs systematic biopsy for the detection of ISUP grade ≥ 2 also in the repeat-biopsy setting.

5.5.3.2 Reduced detection of cancers labelled as ISUP grade group 1

In pooled data of 25 head-to-head comparisons between systematic biopsy and MRI-targeted biopsy, the detection ratio for ISUP grade group 1 cancers was 0.62 (95% CI: 0.44–0.88) in patients with prior negative biopsy and 0.63 (95% CI: 0.54–0.74) in biopsy-naive patients [186]. In the PRECISION and 4M trials, the detection rate of ISUP grade group 1 patients was significantly lower in the MRI-targeted biopsy group as compared to systematic biopsy (9% vs. 22%, p < 0.001, detection ratio of 0.41 for PRECISION; 14% vs. 25%, p < 0.001, detection ratio of 0.56 for 4M) [121, 189]. In the MRI-FIRST trial, MRI-targeted biopsy detected significantly fewer patients with clinically insignificant PCa (defined as ISUP grade group 1 and maximum cancer core length < 6 mm) than systematic biopsy (5.6% vs. 19.5%, p < 0.0001, detection ratio of 0.29) [190]. Consequently, MRI-targeted biopsy without systematic biopsy significantly reduces over-diagnosis of low-risk disease, as compared to systematic biopsy. This seems true even when systematic biopsies are indicated after risk stratification with the Rotterdam Prostate Cancer Risk Calculator) [286].

5.5.3.3 Added value of systematic biopsy and targeted biopsy

From head-to-head comparisons between the two biopsy techniques, it is possible to compute their added value, i.e. the percentage of additional patients with csPCa they contribute to diagnose. Table 5.3 shows the added value of systematic and MRI-targeted biopsy for ISUP grade group ≥ 2 and ≥ 3 cancer detection. The absolute added values in the table refer to the percentage of patients in the entire cohort; if the cancer prevalence is considered, the 'relative' percentage of additional detected csPCa can be computed. Adding MRI-targeted biopsy to systematic biopsy in biopsy-naive patients increases the number of detected ISUP grade ≥ 2 and grade ≥ 3 PCa by approximately 20% and 30%, respectively. In the repeat-biopsy setting, adding MRI-targeted biopsy increases detection of ISUP grade group ≥ 2 and grade group ≥ 3 PCa by approximately 40% and 50%, respectively. Omitting systematic biopsy in biopsy-naive patients would miss approximately 16% of all detected ISUP grade group ≥ 2 PCa and 18% of all ISUP grade ≥ 3 PCa. In the repeat-biopsy setting, it would miss approximately 10% of ISUP grade group ≥ 2 PCa and 9% of ISUP grade group ≥ 3 Pca. The low added value of systematic biopsy in the repeat biopsy setting has been further confirmed by other studies that reported absolute added values of 1.2-3.9% for the detection of ISUP grade group ≥2 cancers and of 1.2-1.6% for ISUP grade group ≥ 3 cancers [191, 312, 313].

Table 5.5: Absolute added values of targeted and systematic biopsies for ISUP grade ≥ 2 and ≥ 3 Cancer Detection

		ISUP ≥ 2			ISUP ≥ 3		
ISUP grade		**Cochrane meta-analysis*** [186]	**MRI-FIRST trial*** [190]	**4M trial** [189]	**Cochrane meta-analysis*** [186]	**MRI-FIRST trial*** [190]	**4M trial** [189]
Biopsy-naïve	Added value of MRI-TBx	6.3% (4.8–8.2)	7.6% (4.6–11.6)	7.0% (ND)	4.7% (3.5–6.3)	6.0% (3.4–9.7)	3.2% (ND)
	Added value of systematic biopsy	4.3% (2.6–6.9)	5.2% (2.8–8.7)	5.0% (ND)	2.8% (1.7–4.8)	1.2% (0.2–3.5)	4.1% (ND)
	Overall prevalence	27.7% (23.7–32.6)	37.5% (31.4–43.8)	30% (ND)	15.5% (12.6–19.5)	21.1% (16.2–26.7)	15% (ND)
Prior negative biopsy	Added value of MRI-TBx	9.6% (7.7–11.8)	-	-	6.3% (5.2–7.7)	-	-
	Added value of systematic biopsy	2.3% (1.2–4.5)	-	-	1.1% (0.5–2.6)	-	-
	Overall prevalence	22.8% (20.0–26.2)	-	-	12.6% (10.5–15.6)	-	-

**Intervals in parenthesis are 95% CI.*

The absolute added value of a given biopsy technique is defined by the percentage of patients of the entire cohort diagnosed only by this biopsy technique.

ISUP = International Society of Urological Pathology (grade); MRI-TBx = magnetic resonance imaging-targeted biopsies; ND = not defined.

Table 5.6: Detection rates of ISUP grade group 1 cancers by targeted and systematic biopsies

Study	Targeted biopsy	Systematic biopsy	p-value
PRECISION [121]	9%	22%	<0.001
PRECISE [188]	10.1	21.7	<0.001
MRI-FIRST [190]*	5.6%	19.5%	<0.0001
4M [189]	14%	24.7%	<0.0001
Cochrane meta-analysis [186]	13.5%	22.4%	<0.01

** In the MRI-FIRST trial, the percentages refer to the detection rates of ISUP 1 cancers with a maximum cancer core length < 6 mm*

5.5.4 ***Perilesional biopsy***

A minimum of three to five cores is required for proper sampling of an MRI detected lesion [313, 314]. Including additional peri-lesional/regional systematic biopsies, rather than standard sextant-based systematic biopsies may decrease the total number of cores taken (by avoiding systematic biopsies in MRI-negative lobes) and improve the detection of csPCa (by compensating for guiding imprecision). In addition, the MRI-targeted and regional biopsy approach could avoid detecting 12-17% of the insignificant cancers detected by the classical combined approach [315-317].

A meta-analysis of eight studies showed a non-significant difference in detection of ISUP grade group ≥2 cancer in the MRI-directed targeted and regional biopsy approach, compared to the recommended practice of MRI-directed targeted- and systematic biopsy approach (RR: 0.95, 95% CI: 0.90–1.01; p = 0.09). However, the MRI-directed targeted- and regional biopsy approach detected significantly more ISUP grade group ≥2 cancers than MRI-targeted biopsy alone (RR: 1.18, 95% CI: 1.10–1.25; p < 0.001) [255]. Other prospective [318] and retrospective [317, 319] studies not included in the meta-analysis provided similar evidence (Table 5.7).

Two studies retrospectively used the location of biopsy cores registered by MRI/US fusion systems to assess the added value of systematic cores based on their distance from the nearest MRI lesion. The diagnostic yield of these systematic cores decreased with increasing distance. Combining the targeted and systematic cores located within a 10 mm and a 15 mm radius from the MR lesions detected 90-92% and 94-97% of the csPCa respectively [315, 316]. The width of the distance from the MRI lesion which enclosed 90% of csPCa may also depend on the PI-RADS score of the lesion; in one series it was found to be 5.5 mm, 12 mm and 16 mm for lesions with PI-RADS scores of 5, 4 and 3 respectively [315]. As a consequence, in men with a PI-RADS 5 index lesion, the absolute added value of additional biopsy has been repeatedly found to be less than 4% for ISUP grade group ≥ 2 cancers and less than 2% for ISUP grade group ≥ 3 cancers [313, 320-322].

5.5.5 ***Prostate MRI and MRI-targeted biopsy reproducibility***

Despite the use of the PI-RADS scoring systems, MRI inter-reader reproducibility remains moderate at best. MRI performance is better with experienced radiologists and at high-volume centres. This currently limits its broad use by non-dedicated radiologists [314, 323].

The accuracy of MRI-targeted biopsy is also substantially impacted by the experience of the biopsy operator [314]. The PRECISE trial, that reproduced the design of the PRECISION trial obtained quite different results. In both trials, the detection rate for ISUP grade group ≥2 PCa was higher for the MRI pathway than for the classical systematic biopsy pathway. Yet, the difference was much lower in the PRECISE trial (+5.2% vs. +12.1% for ISUP grade group ≥2 cancers; +2.1% vs. +5.5% for ISUP grade group ≥3 cancers). In addition, there was major intersite variability in the PRECISE trial: the centre with the highest csPCa detection rate on MRI-targeted biopsy had the lowest on systematic biopsy and vice versa.

These factors of variability give rise to concerns about the reproducibility of the good results of the MRI-directed diagnostic pathways. Efforts towards standardization of the whole diagnostic pathway (MRI acquisition and interpretation, biopsy planning and acquisition) through quality assurance and quality control are currently undertaken [314, 324]. However, significant improvement in the accuracy of MRI and MRI-targeted biopsy can be observed over time through simple measures such as training and participation to MDT meeting with pathological correlation and feedback [314, 325]. Whether artificial intelligence-based assistance will improve MRI interpretation accuracy remains questionable, as preliminary studies reported conflicting results on the topic [326].

5.5.6 ***Cancer grade shift***

MRI findings are significant predictors of adverse pathology features on prostatectomy specimens, and of survival-free BCR after RP or RT [96, 327, 328]. In addition, tumours visible on MRI are enriched in molecular hallmarks of aggressivity, as compared to invisible lesions [329]. Thus, MRI does identify aggressive tumours.

Nonetheless, as MRI-targeted biopsy is more sensitive than systematic biopsy in detecting areas of high-grade cancer, ISUP grade group ≥ 2 cancers detected by MRI-targeted biopsy are, on average, of better prognosis than those detected by the classical diagnostic pathway (Will Rogers phenomenon [98]. This is illustrated in a retrospective series of 1,345 patients treated by RP which showed that, in all risk groups, patients diagnosed by MRI-targeted biopsy had better BCR-free survival than those diagnosed by systematic biopsy only [96]. To mitigate this grade shift, in case of targeted biopsies, the 2019 ISUP consensus conference recommended using an aggregated ISUP grade group summarizing the results of all biopsy cores from the same MR lesion, rather than using the result from the core with the highest ISUP grade group [101] (see pathology section 4.2). When long term follow-up of patients who underwent MRI-targeted biopsy is available, a revision of the risk-groups definition will become necessary. In the meantime, results of MRI-targeted biopsy must be interpreted in the context of this potential grade shift [330].

Table 5.7: Detection rates for ISUP grade group ≥2 prostate cancer achieved by targeted biopsy, combined systematic and targeted biopsy and targeted biopsy with perilesional sampling

	Type of study	Nb of pts	Targeted biopsy with perilesional sampling vs. Combined systematic and targeted biopsy		Targeted biopsy with perilesional sampling vs. Targeted biopsy	
			Ratio of detection rates	Median number of cores	Ratio of detection rates	Median number of cores
Hagens MJ [331]	Meta-analysis	2603	0.95 (0.90 – 1.01), p=0.09	9.5 [7.5-12.3] vs. 16.5 [15.3 – 12.3]	1.18 (1.1 – 1.25), p<0.001	9.5 [7.5 – 12.3] vs. 3.5 [3 – 4]
Hagens MJ [317]	Retrospective, single centre	235	0.968 (0.91 – 0.993)	7 [6 – 9] vs. 12 [10 – 15]	-	-
Hsieh PF, J 18:127 [332]	Prospective, single centre	100	1	15 [12.8 – 18] vs. 26 [23 – 28]	1.20, p=0.008	15 [12.8 – 18] vs. 6 [4 – 7]

5.5.7 Guidelines for MRI imaging in biopsy indication and strategy

Recommendations	Strength rating
Do not use magnetic resonance imaging (MRI) as an initial screening tool.	Strong
Adhere to PI-RADS guidelines for MRI acquisition and interpretation and evaluate MRI results in multidisciplinary meetings with pathological feedback.	Strong
Where MRI has shown a suspicious lesion, MR-targeted biopsy can be obtained through cognitive guidance, US/MR fusion software or direct in-bore guidance.	Weak
Perform MRI before prostate biopsy in men with suspected organ confined disease.	Strong
In men with suspicion of locally advanced disease on digital rectal examination (DRE) and/or prostate-specific antigen (PSA)>50 ng/mL, or those not for curative treatments, consider limited biopsy without MRI.	Weak
When MRI is positive (i.e. PI-RADS ≥ 4), combine targeted biopsy with perilesional sampling.	Weak
When MRI is negative (i.e., PI-RADS ≤ 2), and clinical suspicion of PCa is low (PSA density < 0.20 ng/mL/cc, negative DRE findings, no family history), omit biopsy and offer PSA monitoring; otherwise consider systematic biopsy.	Weak
When MRI is indeterminate (PI-RADS = 3), and clinical suspicion of PCa is very low (PSA density < 0.10 ng/mL/cc, negative DRE findings, no family history), omit biopsy and offer PSA monitoring; otherwise consider targeted biopsy with perilesional sampling.	Weak
If MRI is not available, use a risk calculator and systematic biopsies if indicated.	Strong
When performing systematic biopsy only, at least twelve cores are recommended.	Strong

5.6 Biopsy approach

Ultrasound (US)-guided prostate biopsy is now the standard of care although MRI in-bore biopsy is now possible in a few centres. Ultrasound-guided prostate biopsy can be performed by either the transperineal approach or the transrectal one. Both can be performed under local anaesthesia [333]. However, the only SR and meta-analysis comparing MRI-targeted transrectal biopsy to MRI-targeted transperineal biopsy, analysing 8 studies, showed a higher sensitivity for detection of csPCa when the transperineal approach was used (86% vs. 73%) [334]. This benefit was especially pronounced for anterior tumours. Evidence also suggests reduced infection risk with the transperineal route (see Section 5.2.8.1.1) [335, 336].

5.6.1 Local anaesthesia prior to biopsy

Ultrasound-guided peri-prostatic block is recommended [337]. Ten mL of 2% lidocaine is infiltrated bilaterally along the apex to base. Intra-rectal instillation of local anaesthesia is inferior to peri-prostatic infiltration [338]. Local anaesthesia can also be used effectively for MRI-targeted and systematic transperineal biopsy [339].

Patients are placed in the lithotomy position. Twenty mL of 0.5% bupivacaine with adrenaline (1 in 200,000) is injected into the perineal skin and subcutaneous tissues anterior to the anus, followed two minutes later by a peri-prostatic block. A SR evaluating pain in 3 studies comparing transperineal vs. transrectal biopsies found that the transperineal approach significantly increased patient pain (RR: 1.83 [1.27–2.65]) [340]. In a randomised comparison a combination of peri-prostatic and pudendal block anaesthesia reduced pain during transperineal biopsies compared to peri-prostatic anaesthesia only [341]. Targeted biopsies can then be taken via a brachytherapy grid or a freehand needle-guiding device under local infiltration anaesthesia [339, 342]. Perineal nerve-block was superior for the relief of pain during the biopsy procedure versus periprostatic block (2.80 vs. 3.98; on 1-10 scale) [343].

*5.6.2 **Transperineal prostate biopsy***

A total of eight randomised studies including 1,596 patients compared the impact of biopsy route on infectious complications. Infectious complications were significantly higher following transrectal biopsy (48 events among 789 men) compared to transperineal biopsy (22 events among 807 men) (RR: 95% CI: 2.48 [1.47–4.2]) [344, 345]. In addition, a SR including 165 studies with 162,577 patients described sepsis rates of 0.1% and 0.9% for transperineal and transrectal biopsies, respectively [346]. Finally, a population-based study from the UK (n = 73,630) showed lower re-admission rates for sepsis in patients who had transperineal vs. transrectal biopsies (1.0% vs. 1.4%, respectively) [347]. The available evidence demonstrates that the transrectal approach should be abandoned in favour of the transperineal approach despite any possible logistical challenges. A SR and meta-analysis of eight non-RCTs reported no significant differences between patients receiving or not receiving antibiotic prophylaxis in terms of post-biopsy infection (0,11% vs. 0.31%) and sepsis (0.13% vs. 0,09%), for the transperineal approach [348]. This is in line with another SR and meta-analysis of 112 individual patient cohorts which also showed no significant difference in the number of patients experiencing post-transperineal-biopsy infection 1.35% of 29,880 patients receiving antibiotic prophylaxis and 1.22% of 4,772 men not receiving antibiotic prophylaxis (p = 0.8) [349]. In addition, two published RCTs have reported comparably low post-biopsy infection rates for transperineal biopsy regardless of whether antibiotic prophylaxis was administered or not [350, 351]. A SR and meta-analysis comparing transperineal with and without antibiotic prophylaxis showed very low percentages of septic complications (0.05% vs. 0.08%; p=0.2) and overall infections (1.35% vs. 1.22%; p=0.8)

Thus, there is a growing body of evidence to suggest that antibiotic prophylaxis may not be required for transperineal biopsy; however, the Panel has chosen to wait until a number of ongoing RCTs report their study findings before making a recommendation on this.

*5.6.3 **Transrectal prostate biopsy***

An updated meta-analysis of eleven RCTs including 2,237 men showed that use of a rectal povidone-iodine preparation before biopsy, in addition to antimicrobial prophylaxis, resulted in a significantly lower rate of infectious complications (RR: 95% CI: 0.47 [0.36–0.61]) [345, 352, 353]. Single RCTs showed no evidence of benefit for perineal skin disinfection [354], but reported an advantage for rectal povidone-iodine preparation before biopsy compared to after biopsy [355].

A meta-analysis of four RCTs including 671 men evaluated the use of rectal preparation by enema before transrectal biopsy. No significant advantage was found regarding infectious complications (RR: 95% CI: 0.96 [0.64–1.54]) [345].

An updated meta-analysis of 28 RCTs with 4,027 patients found no evidence that use of periprostatic injection of local anaesthesia resulted in more infectious complications than no injection (RR: 95% CI: 1.08 [0.79–1.48]) [344, 345, 353]. A meta-analysis of nine RCTs including 2,230 patients found that extended biopsy templates showed comparable infectious complications to standard templates (RR: 95% CI: 0.80 [0.53–1.22]) [345]. Additional meta-analyses found no difference in infectious complications regarding needle guide type (disposable vs. reusable), needle type (coaxial vs. non-coaxial), needle size (large vs. small), and number of injections for peri-prostatic nerve block (standard vs. extended) [345].

A meta-analysis of eleven studies with 1,753 patients showed significantly reduced infections after transrectal prostate biopsy when using antimicrobial prophylaxis as compared to placebo/control (RR: 95% CI: 0.56 [0.40–0.77]) [356].

Fluoroquinolones have been traditionally used for antibiotic prophylaxis in this setting; however, in recent years there has been an increase in fluoroquinolone resistance. In addition, the European Commission has implemented stringent regulatory conditions regarding the use of fluoroquinolones resulting in the suspension of the indication for peri-operative antibiotic prophylaxis including prostate biopsy [357].

A SR and meta-analysis on antibiotic prophylaxis for the prevention of infectious complications following prostate biopsy concluded that in countries where fluoroquinolones are allowed as antibiotic prophylaxis, a minimum of a full one-day administration, as well as targeted therapy in case of fluoroquinolone resistance, or augmented prophylaxis (combination of two or more different classes of antibiotics) is recommended [356]. In countries where use of fluoroquinolones are suspended, cephalosporins or

aminoglycosides can be used as individual agents with comparable infectious complications based on meta-analysis of two RCTs [356]. A meta-analysis of three RCTs reported that fosfomycin trometamol was superior to fluoroquinolones (RR: 95% CI: 0.49 [0.27–0.87]) [356], but routine general use should be critically assessed due to the relevant infectious complications reported in non-randomised studies [358]. Of note the indication of fosfomycin trometamol for prostate biopsy has been withdrawn in Germany as the manufacturers did not submit the necessary pharmacokinetic data in support of this indication. Urologists are advised to check their local guidance in relation to the use of fosfomycin trometamol for prostate biopsy. Another possibility is the use of augmented prophylaxis without fluoroquinolones, although no standard combination has been established to date. Finally, targeted prophylaxis based on rectal swap/stool culture is plausible, but no RCTs are available on non-fluoroquinolones. See figure 5.1 for prostate biopsy workflow to reduce infections complications.

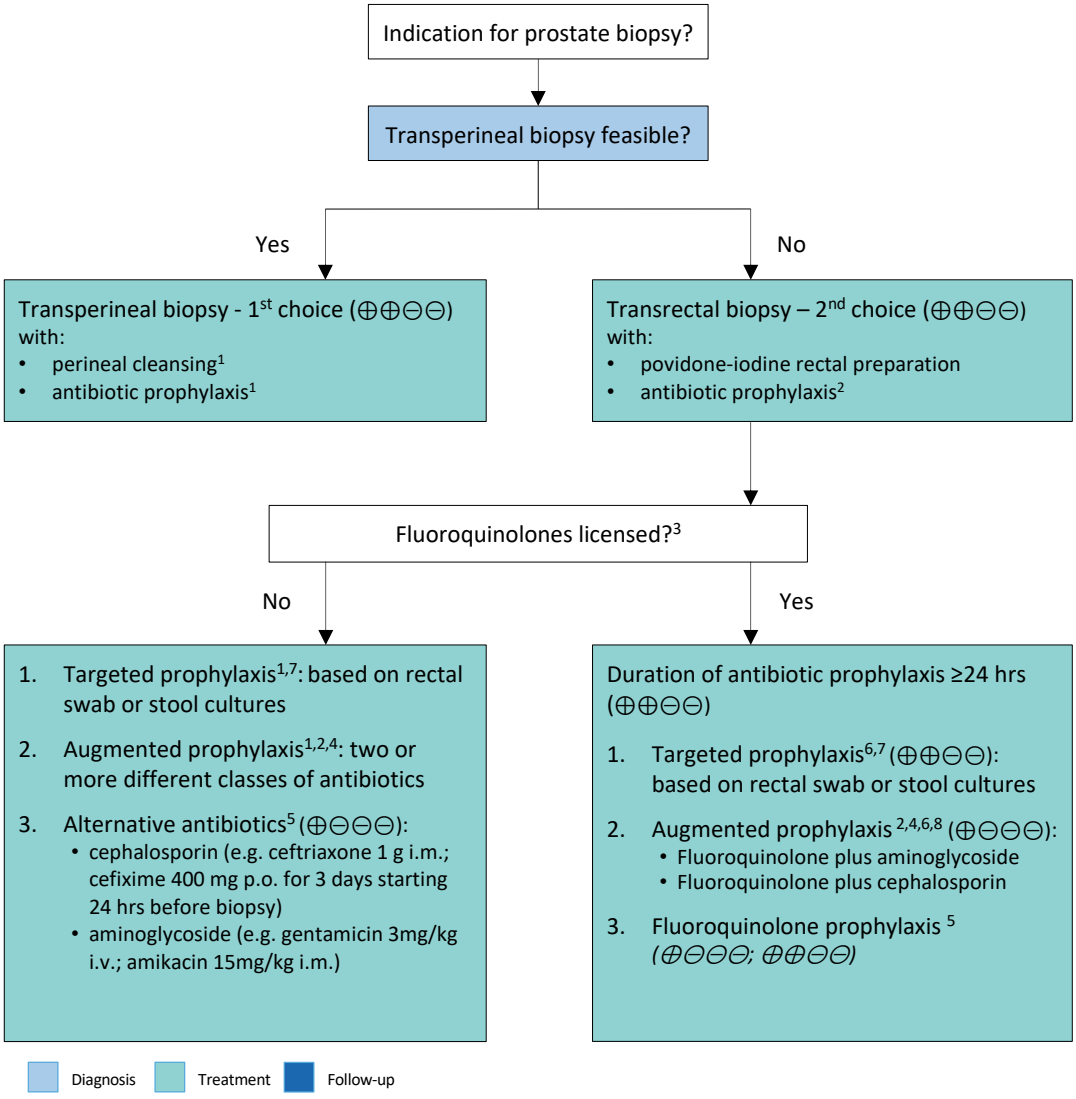
5.6.4 *Summary of evidence and recommendations for performing prostate biopsy (in line with the EAU Urological Infections Guidelines Panel)*

Summary of evidence	LE
A meta-analysis of eight studies including 1,596 patients showed significantly reduced infectious complications in patients undergoing transperineal biopsy as compared to transrectal biopsy.	1a
A meta-analysis of eight non-RCTS reported comparable rates of post-biopsy infections in patients undergoing transperineal biopsy irrespective if antibiotic prophylaxis was given or not.	1a
A meta-analysis of eleven RCTs including 2,036 men showed that use of a rectal povidone-iodine preparation before transrectal biopsy, in addition to antimicrobial prophylaxis, resulted in a significantly lower rate of infectious complications.	1a
A meta-analysis on eleven studies with 1,753 patients showed significantly reduced infections after transrectal biopsy when using antimicrobial prophylaxis as compared to placebo/control.	1a

Recommendations	Strength rating*
Perform prostate biopsy using the transperineal approach due to the lower risk of infectious complications.	Strong
Use routine surgical disinfection of the perineal skin for transperineal biopsy.	Strong
Use rectal cleansing with povidone-iodine prior to transrectal prostate biopsy.	Strong
Use either target prophylaxis based on rectal swab or stool culture; or augmented prophylaxis (two or more different classes of antibiotics); for transrectal biopsy.	Weak
Ensure that prostate core biopsies from different sites are submitted separately for processing and pathology reporting.	Strong

** Note on strength ratings:*
The above strength ratings are explained here due to the major clinical implications of these recommendations. Although data showing the lower risk of infection via the transperineal approach is low in certainty, its statistical and clinical significance warrants its strong rating. Strong ratings are also given for routine surgical disinfection of skin in transperineal biopsy and povidone-iodine rectal cleansing in transrectal biopsy as, although quality of data is low, the clinical benefit is high and practical application simple. A 'Strong' rating is given for avoiding fluoroquinolones in prostate biopsy due to its legal implications in Europe.
*** The indication of fosfomycin trometamol for prostate biopsy has been withdrawn in Germany as the manufacturers did not submit the necessary pharmacokinetic data in support of this indication. Urologists are advised to check their local guidance in relation to the use of fosfomycin trometamol for prostate biopsy.*

Figure 5.2: Prostate biopsy workflow to reduce infectious complications*



Suggested workflow on how to reduce post biopsy infections.
1. Two systematic reviews including non-RCTs and two RCTs describe comparable rates of post-transperineal biopsy infection in patients with and without antibiotic prophylaxis.
2. Be informed about local antimicrobial resistance.
3. Banned by European Commission due to side effects.
4. Contradicts principles of Antimicrobial Stewardship.
5. Only one RCT comparing targeted and augmented prophylaxis.
6. Originally introduced to use alternative antibiotics in case of fluoroquinolone resistance.
7. Various schemes: fluoroquinolone plus aminoglycoside (3 RCTs); and fluoroquinolone plus cephalosporin (1 RCT).

GRADE Working Group grades of evidence. High certainty: (⊕⊕⊕⊕) very confident that the true effect lies close to that of the estimate of the effect. Moderate certainty: (⊕⊕⊕⊖) moderately confident in the effect estimate: the true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different. Low certainty: (⊕⊕⊖⊖) confidence in the effect estimate is limited: the true effect may be substantially different from the estimate of the effect. Very low certainty: (⊕⊖⊖⊖) very little confidence in the effect estimate: the true effect is likely to be substantially different from the estimate of effect. Figure adapted from Pilatz et al., [356] with permission from Elsevier.

** Of note: local guidance in relation to the use of fosfomycin trometamol for prostate biopsy needs to be checked.*

5.6.5 *Complications*

Complications of TRUS biopsy are listed in Table 5.5 [359]. Mortality after prostate biopsy is extremely rare and most are consequences of sepsis [360]. Low-dose aspirin is not an absolute contra-indication [361]. A SR found favourable infection rates for transperineal compared to TRUS biopsies with similar rates of haematuria, haematospermia and urinary retention [362]. A meta-analysis of 4,280 men randomised between transperineal vs. TRUS biopsies in thirteen studies found no significant differences in complication rates, however, data on sepsis compared only 497 men undergoing TRUS biopsy to 474 having transperineal biopsy. The transperineal approach required more (local) anaesthesia [363].

Table 5.8: Adverse events of three groups of targeted biopsy [359] *

	Overall (n = 234)	Transrectal MRI-TB (n = 77)	Transperineal FUS-TB (n = 79)	Transrectal COG-TB (n = 78)	p value
Clavien-Dindo grade					< 0.001
No adverse events	30.3 (71)	47.4 (36)	29.1 (23)	15.4 (12)	
Grade 1	63.2 (148)	50.0 (38)	65.8 (52)	74.4 (58)	
Grade 2	6.0 (14)	2.6 (2)	5.1 (4)	10.3 (8)	
Grades 3, 4, 5	-	-	-	¬-	
Haematuria	53.4 (125)	35.5 (27)	50.6 (40)	74.4 (58)	< 0.001
Haematospermia	37.2 (87)	26.3 (20)	35.4 (28)	50.0 (39)	< 0.01
Rectal bleeding	3.4 (8)	2.6 (2)	2.5 (2)	5.1 (4)	0.59
UTI	3.4 (8)	2.6 (2)	1.3 (1)	6.4 (5)	0.21
Fever	3 (7)	1.3 (1)	2.5 (2)	5.1 (4)	0.46
Urinary retention	3 (7)	-	3.8 (3)	-	0.15
Haematoma	1.3 (3)	-	3.8 (3)	-	0.29
Other					0.56
Lower back pain	0.9 (2)	1.3 (1)	1.3 (1)	-	
Atrial fibrilation	0.4 (1)	-	1.3 (1)	-	

COG-TB = cognitive registration TRUS targeted biopsy; FUS-TB = MRI-TRUS fusion targeted biopsy; MRI = magnetic resonance imaging; MRI-TB = in-bore MRI targeted biopsy; TB = targeted biopsy; TRUS = transrectal ultrasound; UTI = urinary tract infection. Data are presented as % (n).
**With permission by Elsevier.*

5.7 What diagnostic pathway in clinical practice?

The 'combined pathway', in which patients with a positive MRI undergo combined systematic and targeted biopsy, and patients with a negative MRI undergo systematic biopsy, maximises the detection of ISUP grade group ≥2 cancers. However, it has the disadvantage of leading to a greater detection of ISUP grade group 1 cancers and of referring all patients with a clinical suspicion of cancer to biopsy. Given the growing concerns about over-detection of insignificant PCa, the development of AS protocols in patients with ISUP grade group 2 cancers (see section 6.2.1.2.1) and the grade shift induced by MRI-targeted biopsy (see section 5.5.5) the clinical relevance of a diagnostic strategy aimed only at maximising the detection of ISUP grade group ≥ 2 cancers is questionable [364, 365].

The 'MRI pathway' in which patients with a positive MRI undergo only MRI-targeted biopsy and patients with a negative MRI are not biopsied at all could avoid biopsy in 21-49% of the patients if a PI-RADS threshold of ≥3 is used to trigger biopsy [121, 186, 189, 190], at the cost of missing some significant cancers, especially in biopsy-naïve patients or in highly selected populations with high prevalence of csPCa (in which the MRI NPV decreases) [284, 366].

Several alternative MRI-directed diagnostic pathways can be envisaged to correct these limitations, for example by selecting patients for biopsy based on a combination of MRI findings and clinical data or by adding perilesional sampling to MRI-targeted biopsy.

The best pathway remains unclear as prospective evaluations are lacking. Interestingly, in a study different MRI-directed pathways were compared to the classical combined pathway in a retrospective cohort of 499 men. The highest clinical utility above a risk threshold of 6.25% was obtained by a risk-based pathway in which patients with a PI-RADS score of 1-3 and a low-risk profile (PSA-D<0.15 ng/ml/cc, negative DRE, no family history, no ASAP or ISUP1 cancer at prior biopsy) could forgo biopsy while the others underwent combined systematic and

MRI-targeted biopsy. In this pathway, biopsy could have been avoided in 99 men (19%) while missing ISUP grade group ≥ 2 cancers in only 6 men (1.2%) [367].

*5.7.1 **Repeat biopsy after negative biopsy***

During follow-up after negative systematic biopsy, the incidence of PCa is higher, but the risk of PCa death is lower than the population average [368]. Men with prior negative systematic biopsy and persistent suspicion of PCa should have an MRI if not already performed.

Significant PCa may still be present in men with abnormal MRI and negative targeted biopsy [369]. Follow-up or direct repeat biopsy should be considered dependent on risk factors (e.g. PSA density, PIRADS).

In a contemporary series of biopsies the likelihood of finding a csPCa after follow-up biopsy after a diagnosis of atypical small acinar proliferation and high-grade prostatic intraepithelial neoplasia (PIN) was only 6-8%, not significantly different from follow-up biopsies after a negative biopsy [370, 371].

The added value of other biomarkers remains unclear (see Sections 5.2.5.1 and 5.2.5.2).

*5.7.2 **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 [372]. Saturation biopsy may be performed with the transperineal technique, which detects an additional 38% of PCa. The rate of urinary retention varies substantially from 1.2% to 10% [235, 373].

However, given the very low risk of subsequent csPCa after a negative biopsy and/or in case of negative MRI, the clinical utility of saturation biopsy in the repeat biopsy setting remains uncertain in the current MRI-driven diagnostic pathway and such schemes should not be routinely used [374].

*5.7.3 **Seminal vesicle biopsy***

Indications for SV (staging) biopsies are poorly defined. At a PSA of > 15 ng/mL, the odds of tumour involvement are 20–25% [375]. A SV staging biopsy is only useful if it has a decisive impact on treatment, such as ruling out radical tumour resection or for potential subsequent RT. Its added value compared with MRI is questionable.

*5.7.4 **Transition zone biopsy***

Transition zone sampling during baseline biopsies has a low detection rate and should be limited to MRI detected lesions or repeat template biopsies [376].

5.8 Diagnosis - Clinical Staging

*5.8.1 **T-staging***

The cT category listed in Table 4.1 (TNM Classification) only relies on DRE findings. Imaging parameters and biopsy results for local staging are, so far, not part of the T staging (within TNM) and the EAU risk category stratification [377].

5.8.1.1 Ultrasound-based techniques and Computed Tomography

Transrectal US has limited accuracy for PCa local staging [378]. More advanced US-based techniques have not yet been tested in large-scale studies. In case of locally-advanced cancers, abdominopelvic US or CT may show rectal or bladder invasion and dilatation of the upper collecting systems [378].

5.8.1.2 Magnetic Resonance Imaging

T2-weighted imaging remains the most useful method for local staging on MRI. Pooled data from a meta-analysis showed a sensitivity and specificity of 0.57 (95% CI: 0.49–0.64) and 0.91 (95% CI: 0.88–0.93), 0.58 (95% CI: 0.47–0.68) and 0.96 (95% CI: 0.95–0.97), and 0.61 (95% CI: 0.54–0.67) and 0.88 (95% CI: 0.85–0.91), for EPE, SVI, and overall stage T3 assessment, respectively [379]. Detection of EPE and SVI seems more accurate at high field strength (3 Tesla) [379], while the added value of functional imaging remains debated [379, 380].

In 552 men treated by RP at seven different Dutch centres, MRI showed significantly higher sensitivity (51% vs. 12%; $p < 0.001$), and lower specificity (82% vs. 97%; $p < 0.001$) than DRE for non-organ confined disease. All risk groups redefined using MRI findings rather than DRE findings showed better BCR-free survival due to improved discrimination and the Will Roger's phenomenon [381].

Traditionally, EPE/SVI is assessed visually using qualitative signs (e.g., capsular disruption, visible tumour within peri-prostatic fat). Inter-reader agreement with such subjective reading is moderate, with kappa (k) values ranging from 0.41 to 0.68 [382]. The length of tumour capsule contact (LCC) is also a significant predictor of EPE; it has the advantage of being quantitative, although the ideal cut-off value remains debated [383, 384].

Several grading systems combining subjective qualitative signs and/or LCC into a score have shown good sensitivity (0.64–0.82) and specificity (0.64-0.93) for EPE, with substantial inter-reader agreement (κ = 0.56–0.74). None of these scores has shown definitive superiority over the others [385, 386].

Magnetic resonance imaging findings can improve the prediction of the pathological stage when combined with clinical and biopsy data. As a result, several groups developed multivariate risk calculators for predicting EPE/SVI or positive surgical margins [387]. In external validation cohorts, these risk calculators showed significantly better discrimination than nomograms without MRI-based features [388-390]. However, their results must be interpreted with care given potential miscalibration due to varying prevalence of EPE/SVI.

Given its low sensitivity for focal (microscopic) EPE, MRI is not recommended for local staging in low-risk patients. However, MRI can still be useful for treatment planning.

*5.8.2 **N-staging***

5.8.2.1 Computed tomography and MRI

Abdominal CT and T1-T2-weighted MRI indirectly assess nodal invasion by using LN diameter and morphology. However, the size of non-metastatic LNs varies widely and may overlap the size of LN metastases. Usually, LNs with a short axis > 8 mm in the pelvis and > 10 mm outside the pelvis are considered malignant. Decreasing these thresholds improves sensitivity but decreases specificity. As a result, the ideal size threshold remains unclear [391, 392]. Computed tomography and MRI sensitivity is less than 40% [393, 394]. Detection of microscopic LN invasion by CT is < 1% in patients with ISUP grade group < 4 cancer, PSA < 20 ng/mL, or localised disease [391, 395].

Diffusion-weighted MRI (DW-MRI) may detect metastases in normal-sized nodes, but a negative DW-MRI cannot rule out the presence of LN metastases, and DW-MRI provides only modest improvement for LN staging over conventional imaging [396].

5.8.2.2 Risk calculators incorporating MRI findings and clinical data

Because CT and MRI lack sensitivity for direct detection of positive LNs, nomograms combining clinical and biopsy findings have been used to estimate the risk of patients harbouring positive LNs [397-399]. Although these nomograms are associated with good performance, they have been developed using systematic biopsy findings and may therefore not be appropriate for patients diagnosed with combined MRI-targeted biopsy and systematic biopsy.

Two models incorporating MRI-targeted biopsy findings and MRI-derived findings recently underwent external validation [256, 400]. One model was tested on an external cohort of 187 patients with a prevalence of LN invasion of 13.9% (vs. 16.9% in the development cohort). The C-index was 0.73 (vs. 0.81 in the development cohort); at calibration analysis, the model tended to overpredict the actual risk [400]. The Briganti 2019 model was validated in an external multi-centre cohort of 487 patients with a prevalence of 8% of LN invasion (vs. 12.5% in the development cohort). The AUC was 0.79 (vs. 0.81 in the development cohort). Using a risk cut-off of 7% would have avoided LN dissection in 273 (56% of the cohort), while missing LN invasion in seven patients (2.6% of the patients below the 7% threshold; 18% of the 38 patients with LN invasion) [401]. Another cohort of 150 high-risk patients with a LN invasion prevalence of 26% was retrospectively used to externally assess four different nomograms. All showed high sensitivity (>0.95) and low specificity (<0.19) at the tested thresholds. Using the 7% threshold, the Briganti 2019 nomogram had a sensitivity of 0.96 and a specificity of 0.18 [402]. The calibration of the nomogram will be affected by the prevalence of LN involvement in your population.

5.8.2.3 Choline PET/CT

In a meta-analysis of 609 patients, pooled sensitivity and specificity of choline PET/CT for pelvic LN metastases were 62% (95% CI: 51–66%) and 92% (95% CI: 89–94%), respectively [403]. In a prospective trial of 75 patients at intermediate risk of nodal involvement (10–35%), the sensitivity was only 8.2% at region-based analysis and 18.9% at patient-based analysis, which is too low to be of clinical value [404]. The sensitivity of choline PET/CT increases to 50% in patients at high risk and to 71% in patients at very high risk [405].

5.8.2.4 Prostate-specific membrane antigen-based PET/CT

Prostate-specific membrane antigen PET/CT uses several different radiopharmaceuticals; most published studies used 68Ga-labelling for PSMA PET imaging, but some used 18F-labelling (e.g., 18F-DCFPyL,

18F-PSMA-1007, 18F-PSMA-JK-7). PSMA is also an attractive target because of its specificity for prostate tissue, even if the expression in other non-prostatic malignancies or benign conditions may cause incidental false-positive findings [406, 407].

A multi-centre prospective phase III imaging trial, investigating men with intermediate- and high-risk PCa who underwent RP and PLND, showed a sensitivity and specificity of 68Ga-PSMA-11 PET of 0.40 (95% CI: 0.34-0.46), and 0.95 (95% CI: 0.92-0.97), respectively [408]. This is line with previous results from prospective, multi-centre studies addressing the accuracy of 68Ga-PSMA and 18F-DCFPyL PET/CT for LN staging in patients with newly diagnosed PCa [409, 410]. Comparable results were also demonstrated in a phase II/III prospective, multi-centre study (OSPREY) with a median specificity of 97.9% (95% CI: 94.5–99.4%) and median sensitivity of 40.3% (28.1–52.5%) for pelvic nodal involvement [411]. Prostate-specific antigen may be a predictor of a positive PSMA PET/CT. In the primary staging cohort from a meta-analysis, however, no robust estimates of positivity were found [412].

Comparison between PSMA PET/CT and MRI was performed in a SR and meta-analysis including 13 studies (n = 1,597) [413]. 68Ga-PSMA was found to have a higher sensitivity and a comparable specificity for staging pre-operative LN metastases in intermediate- and high-risk PCa [414].

Prostate specific membrane antigen PET/CT has a good sensitivity and specificity for LN involvement, possibly impacting clinical decision-making. In a review and meta-analysis including 37 articles, a subgroup analysis was performed in patients undergoing PSMA PET/CT for primary staging. On a per-patient-based analysis, the sensitivity and specificity of 68Ga-PSMA PET were 77% and 97%, respectively, after eLND at the time of RP. On a per-lesion based analysis, sensitivity and specificity were 75% and 99%, respectively [412].
In summary, PSMA PET/CT is more sensitive in N-staging as compared to MRI, abdominal contrast-enhanced CT or choline PET/CT. However, small LN metastases, under the spatial resolution of PET, may still be missed.

5.8.2.5 Risk calculators incorporating MRI and PSMA findings

An international, multi-centre study incorporated PSMA PET into existing nomograms in order to predict pelvic LN metastatic disease in PCa patients. Performance of three nomograms was assessed in 757 patients undergoing RARP and ePLND. Addition of PSMA PET to the nomograms substantially improved the discriminative ability of the models yielding cross-validated AUCs of 0.76 (95% CI: 0.70–0.82), 0.77 (95% CI: 0.72–0.83), and 0.82 (95% CI: 0.76–0.87), respectively [415].

*5.8.3 **M-staging***

5.8.3.1 Bone scan

^{99m}Tc-Bone scan is a highly sensitive conventional imaging technique, evaluating the distribution of active bone formation in the skeleton related to malignant and benign disease. A meta-analysis showed combined sensitivity and specificity of 79% (95% CI: 73–83%) and 82% (95% CI: 78–85%) at patient level [416]. Bone scan diagnostic yield is significantly influenced by the PSA level, the clinical stage and the tumour ISUP grade group [391, 417]. A retrospective study investigated the association between age, PSA and GS in 703 newly diagnosed PCa patients who were referred for bone scintigraphy. The incidence of bone metastases increased substantially with rising PSA and upgrading GS [418]. In two studies, a dominant Gleason pattern of 4 was found to be a significant predictor of positive bone scan [419, 420]. Bone scanning should be performed in symptomatic patients, independent of PSA level, ISUP grade group or clinical stage [391].

5.8.3.2 Fluoride PET/CT, choline PET/CT and MRI

^{18}F-sodium fluoride (^{18}F-NaF) PET or PET/CT, similarly to bone scintigraphy, only assesses the presence of bone metastases. The tracer was reported to have similar specificity and superior sensitivity to bone scintigraphy for detecting bone metastases in patients with newly diagnosed high-risk PCa [421, 422]. Interobserver agreement for the detection of bone metastases was excellent, demonstrating that 18F-NaF PET/CT is a robust tool for the detection of osteoblastic lesions in patients with PCa [423].

It remains unclear whether choline PET/CT is more sensitive than bone scan but it has higher specificity with fewer indeterminate bone lesions [424-426]. Choline PET/CT has also the advantage of detecting visceral and nodal metastases.

Diffusion-weighted whole-body and axial skeleton MRI are more sensitive than bone scan and targeted conventional radiography in detecting bone metastases in high-risk PCa. Whole-body MRI can also detect visceral and nodal metastases; it was shown to be more sensitive and specific than combined bone scan, targeted radiography and abdominopelvic CT [427]. A meta-analysis found that whole-body MRI is more sensitive than choline PET/CT and bone scan for detecting bone metastases on a per-patient basis, although choline PET/CT had the highest specificity [416].

5.8.3.3 *PSMA PET/CT*

A SR including twelve studies (n = 322) reported high variation in ^{68}Ga-PSMA PET/CT sensitivity for initial staging (range 33–99%; median sensitivity on per-lesion analysis 33–92%, and on per-patient analysis 66–91%), with good specificity (per-lesion 82–100%, and per-patient 67–99%), with most studies demonstrating increased detection rates with respect to conventional imaging modalities (bone scan and CT) [428].

In a prospective multi-centre study in patients with high-risk PCa before curative surgery or RT (proPSMA), 302 patients were randomly assigned to conventional imaging or ^{68}Ga-PSMA-11 PET/CT [429]. The primary outcome focused on the accuracy of first-line imaging for the identification of pelvic LN or distant metastases. Accuracy of ^{68}Ga-PSMA PET/CT was 27% (95% CI: 23–31) higher than that of CT and bone scintigraphy (92% [95% CI: 88–95] vs. 65% [95% CI: 60–69]; p < 0.0001). Conventional imaging had a lower sensitivity (38% [95% CI: 24–52] vs. 85% [95% CI: 74–96]) and specificity (91% [95% CI: 85–97] vs. 98% [95% CI: 95–100]) than PSMA PET/CT. Furthermore, ^{68}Ga-PSMA PET/CT scan prompted management change more frequently as compared to conventional imaging (41 [28%] men [95% CI: 21–36] vs. 23 [15%] men [95% CI: 10–22], p = 0.08), with less equivocal findings (7% [95% CI: 4–13] vs. 23% [95% CI: 17–31]) and lower radiation exposure (8.4 mSv vs. 19.2 mSv; p < 0.001) [429].The comparison of whole body MRI and PSMA PET/CT in detecting bone metastases has led to inconclusive opposite results in two small cohorts [414, 430].

5.8.4 ***Summary of evidence and practical considerations on initial N/M staging***

The field of non-invasive N- and M-staging of PCa patients is evolving very rapidly. Evidence shows that choline PET/CT, PSMA PET/CT and whole-body MRI provide a more sensitive detection of LN- and bone metastases than the classical work-up with bone scan and abdominopelvic CT. In view of the evidence offered by the randomised, multi-centre proPSMA trial [429], replacing bone scan and abdominopelvic CT by more sensitive imaging modalities may be a consideration in patients with high-risk PCa undergoing initial staging. However, in absence of prospective studies demonstrating survival benefit, caution must be used when taking therapeutic decisions [431]. The prognosis and ideal management of patients diagnosed as metastatic by these more sensitive tests is unknown. In particular, it is unclear whether patients with metastases detectable only with PET/CT or whole-body MRI should be managed using systemic therapies only, or whether they should be subjected to aggressive local and metastases-directed therapies [432].

Results from RCTs evaluating the management and outcome of patients with (and without) metastases detected by choline PET/CT, PSMA PET/CT and MRI are awaited before a recommendation can be made to treat patients based on the results of these tests.

5.8.5 ***Summary of evidence and guidelines for staging of prostate cancer***

Recommendations	Strength rating
Any risk group staging	
Use pre-biopsy magnetic resonance imaging (MRI) for local staging information.	Weak
Low-risk localised disease	
Do not use additional imaging for staging purposes.	Strong
Intermediate-risk disease	
For patients with International Society of Urological Pathology (ISUP) grade group 3 disease, include at least cross-sectional abdominopelvic imaging and a bone-scan for metastatic screening.	Weak
Perform prostate-specific antigen-positron emission tomography/computed tomography (PSMA-PET/CT) if available to increase accuracy.	Weak
High-risk localised disease/locally advanced disease	
Perform metastatic screening using PSMA-PET/CT if available and at least cross-sectional abdominopelvic imaging and a bone-scan.	Strong

6. TREATMENT

This chapter reviews the available treatment modalities, followed by separate sections addressing treatment for the various disease stages.

6.1 Estimating life expectancy and health status

6.1.1 ***Introduction***

Evaluation of life expectancy and health status is important in clinical decision-making for early detection, diagnosis, and treatment of PCa. Prostate cancer is common in older men (median age 68) and diagnoses in men > 65 will result in a 70% increase in annual diagnosis by 2030 in Europe and the USA [433, 434].

Active treatment mostly benefits patients with intermediate- or high-risk PCa and longest expected survival. In localised disease, over ten years life expectancy is considered mandatory for any benefit from local treatment and an improvement in CSS may take longer to become apparent. Older age and worse baseline health status have been associated with a smaller benefit in PCSM and life expectancy of surgery vs. AS [435]. Although in a RCT the benefit of surgery with respect to death from PCa was largest in men < 65 years of age (RR: 0.45), RP was associated with a reduced risk of metastases and use of androgen deprivation therapy (ADT) also among older men (RR: 0.68 and 0.60, respectively) [436]. External beam RT shows similar cancer control regardless of age, assuming a dose of > 72 Gy when using intensity-modulated or image-guided RT [437].

Older men have a higher incidence of PCa and may be under-treated despite the high overall mortality rates [438, 439]. Of all PCa-related deaths 71% occur in men aged > 75 years [440], probably due to the higher incidence of advanced disease and death from PCa despite higher death rates from competing causes [441-443]. In the USA, only 41% of patients aged > 75 years with intermediate- and high-risk disease received curative treatment compared to 88% aged 65–74 [444].

6.1.2 ***Life expectancy***

Life expectancy tables for European men are available online: https://ec.europa.eu/eurostat/. Survival may be variable and therefore estimates of survival must be individualised. Gait speed is a good single predictive method of life expectancy (from a standing start, at usual pace, generally over 6 meters). For men at age 75, ten-year survival ranged from 19% < 0.4 m/s to 87%, for ≥ 1.4 m/s [445].

Figure 6.1: Predicted Median Life Expectancy by Age and Gait Speed for males* [445]

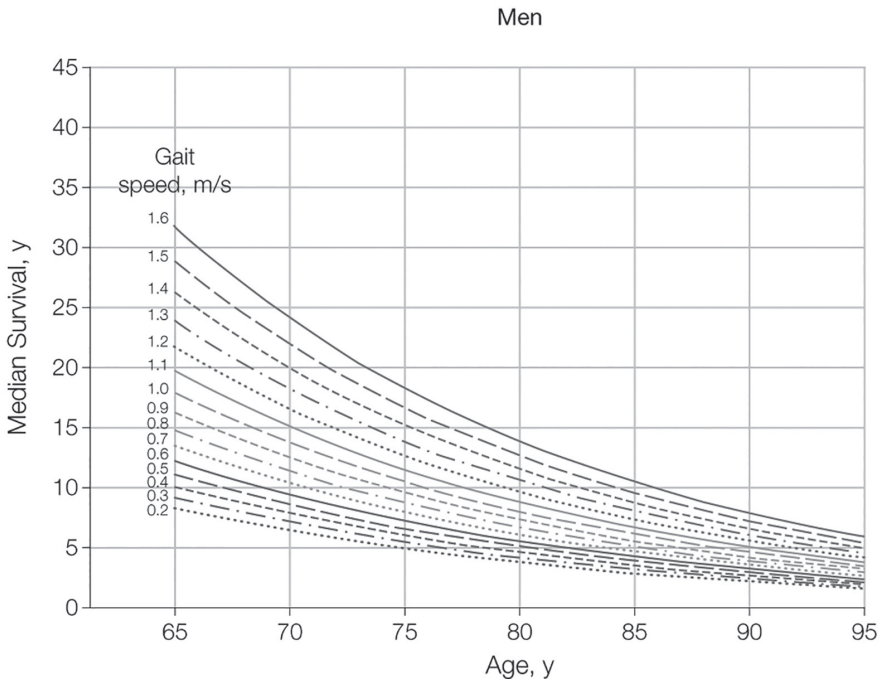


**Figure reproduced with permission of the publisher, from Studenski S, et al. JAMA 2011 305(1)50.*

*6.1.3 **Health status screening***

Heterogeneity in performance increases with advancing age, so it is important to use measures other than just age or performance status (PS) when considering treatment options. The International SIOG PCa Working Group recommends that treatment for adults over 70 years of age should be based on a systematic evaluation of health status using the G8 (Geriatric 8) screening tool (see Table 5.7) [136]. This tool helps to discriminate between those who are fit and those with frailty, a syndrome of reduced ability to respond to stressors. Patients with frailty have a higher risk of mortality and negative side effects of cancer treatment [446]. Healthy patients with a G8 score > 14 or vulnerable patients with reversible impairment after resolution of their geriatric problems should receive the same treatment as younger patients. Frail patients with irreversible impairment should receive adapted treatment. Patients who are too ill should receive only palliative treatment (see Figure 5.3) [136]. Patients with a G8 score ≤ 14 should undergo a comprehensive geriatric assessment (CGA) as this score is associated with three-year mortality. A CGA is a multi-domain assessment that includes co-morbidity, nutritional status, cognitive and physical function, and social supports to determine if impairments are reversible [447]. A SR of the effect of geriatric evaluation for older cancer patients showed improved treatment tolerance and completion [448].

The Clinical Frailty Scale (CFS) is another screening tool for frailty (see Figure 5.4) [449]. Although not frequently used in the cancer setting, it is considered to be a common language for expressing degree of frailty. The scale runs from one to nine, with higher scores indicating increasing frailty. Patients with a higher CFS score have a higher 30-day mortality after surgery and are less likely to be discharged home [450].

It is important to use a validated tool to identify frailty, such as the G8 or CFS, as clinical judgement has been shown to be poorly predictive of frailty in older patients with cancer [451].

6.1.3.1 Co-morbidity

Co-morbidity is a major predictor of non-cancer-specific death in localised PCa treated with RP and is more important than age [452, 453]. Ten years after watchful waiting for PCa, most men with a high co-morbidity score had died from competing causes, irrespective of age or tumour aggressiveness [452]. Measures for co-morbidity include: Cumulative Illness Score Rating-Geriatrics (CISR-G) [454, 455] (Table 5.8) and Charlson Co-morbidity Index (CCI) [456].

6.1.3.2 Nutritional status

Malnutrition can be estimated from body weight during the previous three months (good nutritional status < 5% weight loss; risk of malnutrition: 5–10% weight loss; severe malnutrition: > 10% weight loss) [457].

6.1.3.3 Cognitive function

Cognitive impairment can be screened for using the mini-COG (https://mini-cog.com/) which consists of three-word recall and a clock-drawing test and can be completed within five minutes. A score of ≤ 3/5 indicates the need to refer the patient for full cognitive assessment. Patients with any form of cognitive impairment (e.g., Alzheimer's or vascular dementia) may need a capacity assessment of their ability to make an informed decision, which is an increasingly important factor in health status assessment [458-460]. Cognitive impairment also predicts risk of delirium, which is important for patients undergoing surgery [461].

6.1.3.4 Physical function

Measures for overall physical functioning include: Karnofsky score and ECOG scores [462]. Measures for dependence in daily activities include Activities of Daily Living (ADL; basic activities) and Instrumental Activities of Daily Living (IADL; activities requiring higher cognition and judgement) [463-465].

6.1.3.5 Shared decision-making

The patient's own values and preferences should be considered as well as the above factors. A shared decision-making process also involves anticipated changes to QoL, functional ability, and a patient's hopes, worries and expectations about the future [466]. Particularly in older and frail patients, these aspects should be given equal importance to disease characteristics during the decision-making process [467]. Older patients may also wish to involve family members, and this is particularly important where cognitive impairment exists.

*6.1.4 **Conclusion***

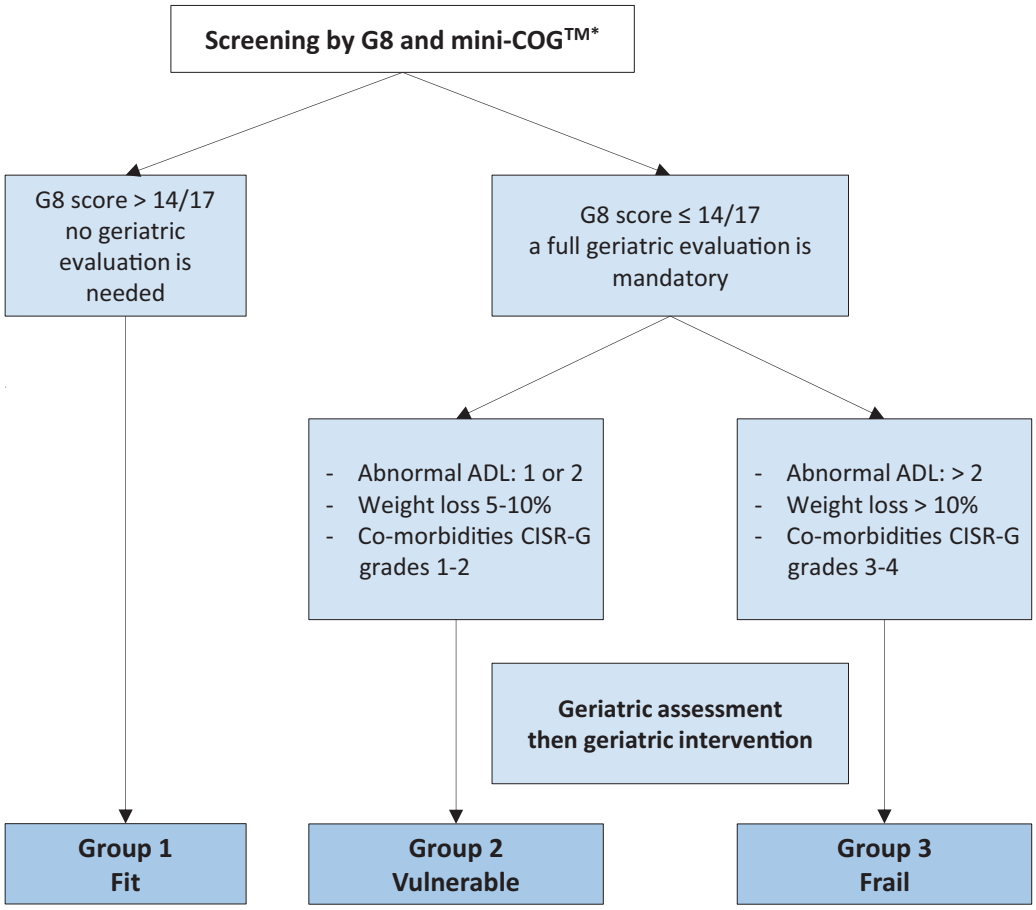
Individual life expectancy, health status, frailty, and co-morbidity, not only age, should be central in clinical decisions on screening, diagnostics, and treatment for PCa. A life expectancy of ten years is most commonly used as a threshold for benefit of local treatment. Older men may be under-treated. Patients aged 70 years of age or older who have frailty should receive a comprehensive geriatric assessment. Resolution of impairments in vulnerable men allows a similar urological approach as in fit patients.

Table 6.1: G8 screening tool (adapted from [468]**)**

	Items	**Possible responses (score)**
A	Has food intake declined over the past three 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 three 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
D	Neuropsychological problems?	0 = severe dementia or depression
		1 = mild dementia
		2 = no psychological problems
E	BMI? (weight in kg)/(height in m^2)	0 = BMI < 19
		1 = BMI 19 to < 21
		2 = BMI 21 to < 23
		3 = BMI ≥ 23
F	Takes more than three prescription drugs per day?	0 = yes
		1 = no

G	In comparison with other people of the same age, how does the patient consider his/her health status?	0.0 = not as good
		0.5 = does not know
		1.0 = as good
		2.0 = better
H	Age	0 = ≥ 85
		1 = 80-85
		2 = < 80
	Total score	**0-7**

Figure 6.2: Decision tree for health status screening (men > 70 years)** [136]



Mini-COGTM = Mini-COGTM cognitive test; ADLs = activities of daily living; CIRS-G = Cumulative Illness Rating Score - Geriatrics; CGA = comprehensive geriatric assessment.
** For Mini-COGTM, a cut-off points of ≤ 3/5 indicates a need to refer the patient for full evaluation of potential dementia.*
***Reproduced with permission of Elsevier, from Boyle H.J., et al. Eur J Cancer 2019:116; 116 [136].*

Figure 6.3: The Clinical Frailty Scale version 2.0 [449]*

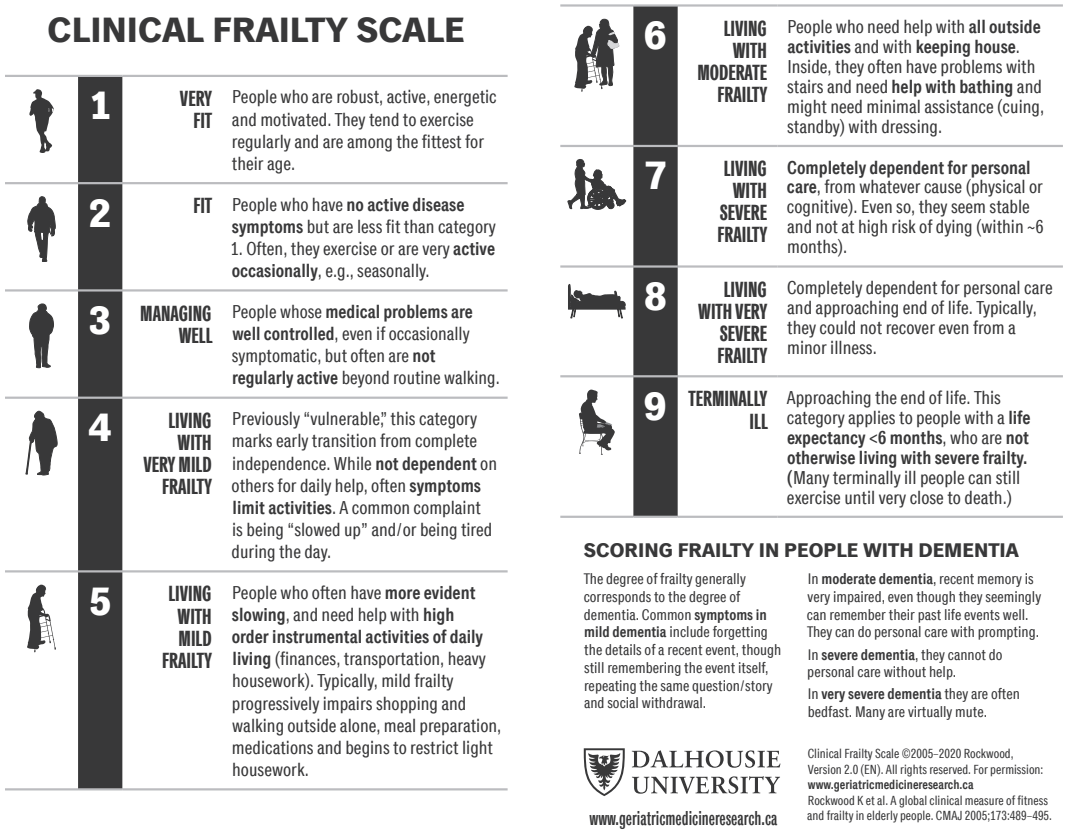


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Table 6.2: Cumulative Illness Score Rating-Geriatrics (CISR-G)

1	Cardiac (heart only)
2	Hypertension (rating is based on severity; affected systems are rated separately)
3	Vascular (blood, blood vessels and cells, marrow, spleen, lymphatics)
4	Respiratory (lungs, bronchi, trachea below the larynx)
5	ENT (eye, ear, nose, throat, larynx)
6	Upper GI (esophagus, stomach, duodenum. Biliar and parcreatic trees; do not include diabetes)
7	Lower GI (intestines, hernias)
8	Hepatic (liver only)
9	Renal (kidneys only)
10	Other GU (ureters, bladder, urethra, prostate, genitals)
11	Musculo-Skeletal-Integumentary (muscles, bone, skin)
12	Neurological (brain, spinal cord, nerves; do not include dementia)
13	Endocrine-Metabolic (includes diabetes, diffuse infections, infections, toxicity)
14	Psychiatric/Behavioural (includes dementia, depression, anxiety, agitation, psychosis)
	All body systems are scores on a 0 - 4 scale. - 0: No problem affecting that system. - 1: Current mild problem or past significant problem. - 2: Moderate disability or morbidity and/or requires first line therapy. - 3: Severe problem and/or constant and significant disability and/or hard to control chronic problems. - 4: Extremely severe problem and/or immediate treatment required and/or organ failure and/or severe functional impairment.
Total score 0-56	

6.1.5 *Guidelines for evaluating health status and life expectancy*

Recommendations	Strength rating
Use individual life expectancy, health status, and co-morbidity in PCa management.	Strong
Use the Geriatric-8, mini-COG and Clinical Frailty Scale tools for health status screening.	Strong
Perform a full specialist geriatric evaluation in patients with a G8 score ≤ 14.	Strong
Consider standard treatment in vulnerable patients with reversible impairments (after resolution of geriatric problems) similar to fit patients, if life expectancy is > ten years.	Weak
Offer adapted treatment or watchful waiting to patients with irreversible impairment.	Weak
Offer palliative symptom-directed therapy alone to frail patients.	Strong

6.2 Treatment modalities

6.2.1 *Deferred treatment (watchful waiting/active surveillance)*

As the prevalence of cancer cells in the prostate is so much higher than the risk of dying from PCa, together with the increased rate of early detection of small tumours after the introduction of PSA, there is a distinct risk of over-diagnosis and subsequent over-treatment of the disease (Chapter 3.1 Epidemiology) [8, 12, 469]. All available radical PCa treatment options may cause significant side effects so conservative treatment options are needed for patients with a low risk of PCa death or symptomatic progression from their PCa. Data from studies conducted on patients who did not undergo local treatment with up to 25 years of follow-up, with endpoints of OS and CSS, are available. Several series have shown a consistent CSS rate of 82–87% at ten years [470, 471], and 80–95% for T1/T2 and ISUP grade group ≤ 2 PCas [472]. In three studies with data beyond 15 years, the CSS was 80%, 79% and 58% respectively [470, 471, 473], and two reported 20-year CSS rates of 57% and 32% [470, 473]. The observed heterogeneity in outcomes is due to different inclusion criteria, with some older studies from the pre-PSA era showing worse outcomes [473]. In addition, many patients classified as ISUP grade group 1 would now be classified as ISUP grade group 2–3 based on the 2005 Gleason classification, suggesting that the above-mentioned results should be considered as minimal and current outcomes would be more favourable. Patients with well-, moderately- and poorly-differentiated tumours had 10-year CSS rates of 91%, 90% and 74%, respectively, correlating with data from a pooled analysis [472]. In screen-detected localised PCa there is also a lead-time bias, resulting in a higher rate of early detected PCa, but also an even higher risk of detecting clinically insignificant PCa that never would have caused any problems [469]. Cancer-specifc survival from untreated screen-detected PCa in patients with ISUP grade groups 1–2 is therefore likely to be even more favourable than for PCa detected of other reasons. Consequently, a high proportion of men with PSA-detected PCa are suitable for conservative management such as active surveillance (AS) or watchful waiting (WW). As the decision to choose WW is more independent from the tumour stage, and mainly dependent on patient factors/life expectancy, this approach may include patients of all ISUP grade groups (see Chapter 6.2.1.1).

The high CSS rates of localised PCa requires that a life expectancy of at least ten years should be considered mandatory for any benefit from active treatment. Co-morbidity is as important as age in predicting life expectancy in men with PCa. Increasing co-morbidity greatly increases the risk of dying from non-PCa-related causes. In an analysis of 19,639 patients aged > 65 years who were not given curative treatment, most men with a CCI score ≥ 2 had died from competing causes at ten years follow-up regardless of their age at time of diagnosis. Tumour aggressiveness had little impact on OS suggesting that patients could have been spared biopsy and diagnosis of cancer. Men with a CCI score ≤ 1 had a low risk of death at ten years, especially for well- or moderately-differentiated lesions [452]. Additionally, in the ProtecT trial (see 6.2.1.2), prostate cancer-related death was 3% at 15 years compared to death from any cause in 21.7% of patients, numbers that have been further validated in two large population-based studies from Canada and Sweden [474-476]. Estimation of competing benefits of active versus conservative treatment and death from any cause at ten and 15 years can be estimated using the PREDICT Prostate tool (available from https://prostate.predict.nhs.uk/), which was developed using registry data from the UK with external validation and is endorsed by the National Institute for Health and Care Excellence in the UK [477]. This highlights the importance of assessing co-morbidity even before considering a biopsy, but also before advising a patient with a PCa diagnosis on the optimal treatment for him.

There are two distinct strategies for conservative management that aim to reduce over-treatment: AS and WW (Table 6.2.1).

Table 6.2.1: Definitions of active surveillance and watchful waiting [478]

	Active surveillance	Watchful waiting
Treatment intent	Curative	Palliative
Follow-up	Pre-defined schedule	Patient-specific
Assessment/markers* used	DRE, PSA, MRI at recruitment, re-biopsy	Annual (biannual) PSA and DRE if significant PSA-rise
Life expectancy	> ten years	< ten years
Aim	Minimise treatment-related toxicity without compromising survival, as the PCa is so indolent that it is unlikely to cause symptoms even with long life expectancy	Minimise treatment-related toxicity without compromising survival, as the lifespan is so limited that PCa is unlikely to cause symptoms
Eligible patients	Low- and selected intermediate-risk patients	Can apply to patients with all stages

DRE = digital rectal examination; PSA = prostate-specific antigen; MRI = magnetic resonance imaging.

**Molecular markers and/or PSMA-PET/CT (-MRI) may be used.*

6.2.1.1 Watchful Waiting

Watchful waiting refers to conservative management for patients deemed unsuitable for curative treatment from the outset. The aim of WW is to balance the potential harms and benefits of early hormonal treatment, and patients are clinically 'watched' for the development of local or systemic progression with (imminent) disease-related complaints, at which stage they are then treated palliatively according to their symptoms in order to maintain QoL. Traditionally WW has meant waiting for symptoms of the tumour to develop and has, in some practices, not included regular follow-up in any active way. However, today we have evidence that early hormonal treatment could prolong short term survival (within a few years) for locally advanced disease, for patients with a PSAdt < twelve months, and for PSA-values over 30-50 ng/ml [479, 480]. A more active follow-up of men on WW could therefore be beneficial, so that a local progression (often associated with a higher ISUP grade group), or start of metastatic spread, can be detected before they present with significant symptoms. Hormonal treatment could then be considered before symptoms emerge. The WW strategy should therefore be individualised and planned together with the patient. Biannual PSA, or annual after a period of stable disease, followed by DRE if PSA rises significantly, could then be of value, especially for men with a life expectancy > five years but unsuitable for curative treatment. There are two RCTs and one Cochrane review comparing the outcomes of WW to RP. The SPCG-4 study was a RCT from the pre-PSA era, randomising patients to either WW or RP [481]. The study found RP to provide superior CSS, OS and progression-free survival (PFS) compared to WW at a median follow-up of 23.6 years (range 3 weeks–28 years). However, the benefit in favour of RP over WW was only apparent after ten years. The PIVOT trial, a RCT conducted in the early PSA era, made a similar comparison between RP vs. WW in 731 men (50% with nonpalpable disease) but in contrast to the SPCG-4, it found little, to no, benefit of RP (cumulative incidence of all-cause death, RP vs. observation: 68% vs. 73%; RR: 0.92, 95% CI: 0.84–1.01) within a median follow-up period of 18.6 years (interquartile range, 16.6 to 20 years) [482]. Exploratory subgroup analysis showed that the borderline benefit from RP was most marked for intermediate-risk disease (RR: 0.84, 95% CI: 0.73–0.98) but there was no benefit in patients with low- or high-risk disease. Overall, no adverse effects on health related QoL (HRQoL) and psychological well-being was apparent in the first five years [483]. However, one of the criticisms of the PIVOT trial is the relatively high overall mortality rate in the WW group compared with more contemporary series. A Cochrane review performed a pooled analysis of RCTs comparing RP vs. WW [484]. Three studies were included; the previously mentioned SPCG-4 [481] and PIVOT [482] and the Veteran's Administration Cooperative Urological Research Group (VACURG) study which was conducted in the pre-PSA era [485]. The authors found that RP compared with WW reduced time to death by any cause (HR: 0.79, 95% CI: 0.70–0.90), time to death by PCa (HR: 0.57, 95% CI: 0.44–0.73) and time to metastatic progression (HR: 0.56, 95% CI: 0.46–0.70) at 29 years' follow-up. However, RP was associated with higher rates of urinary incontinence (RR: 3.97, 95% CI: 2.34–6.74) and ED (RR: 2.67, 95% CI: 1.63–4.38).

The overall evidence indicates that for men with asymptomatic, clinically localised PCa, and with a life expectancy of < ten years based on comorbidities and/or age, the oncological advantages of active treatment over WW are unlikely to be relevant to them. Consequently, WW should be adopted for such patients. For assistance in estimating life expectancy and health status see Section 5.4.

6.2.1.2 Active surveillance

Active surveillance aims to delay or completely avoid unnecessary treatment, and consequently unnecessary side effects, in men with clinically localised PCa, and a life expectancy of ten years or more, who do not require immediate treatment, but at the same time achieve the correct timing for curative treatment in those who eventually do [486]. Patients remain under close surveillance through structured surveillance programmes with regular follow-up consisting of PSA testing, clinical examination, MRI imaging and repeat prostate biopsies, with curative treatment being prompted by pre-defined thresholds indicative of development to potentially significant disease, which is still curable, while considering individual life expectancy.

No formal RCT is available comparing AS to curative treatment. Several cohorts have investigated AS in organ-confined disease, the findings of which were summarised in a SR [487]. A largest prospective series of men with low-risk PCa managed by AS was published [488]. Table 6.1.2 summarises the results of selective AS cohorts. It is clear that the long-term OS and CSS of patients on AS are extremely good. However, more than one-third of patients are 'reclassified' during follow-up, most of whom undergo curative treatment due to disease upgrading, increase in disease extent, disease stage, progression, or patient preference. There is considerable variation and heterogeneity between studies regarding patient selection and eligibility, follow-up policies (including frequency and type of imaging such as MRI imaging, type and frequency of repeat prostate biopsies, such as MRI-targeted biopsies or transperineal template biopsies, use of PSA kinetics and density, and frequency of clinical follow-up), when active treatment should be instigated (i.e., reclassification criteria) and which outcome measures should be prioritised [486]. For specific guidelines on inclusion criteria and follow-up strategies for AS, see Sections 6.2.1.2.

In the ProtecT RCT, 1,643 patients were randomised into one of three arms: active treatment with either RP or EBRT or AM with outcomes reported at ten years and 15 years [474, 489]. Even though the ProtecT trial is a RCT it is not, strictly speaking, a study comparing AS to active treatment as it does not include a formal AS strategy as described above and in Sections 6.2.1.2. Active monitoring (AM), as used in the study, was a significantly less stringent surveillance strategy in terms of clinical follow-up, using PSA only, with relaxed criteria to define progression. No imaging and repeat biopsies were performed as in AS. At enrolment fifty-six percent of the patients had low-risk disease, with 90% having a PSA < 10 ng/mL, 77% ISUP grade group 1 (20% ISUP grade group 2–3), and 76% had T1c disease. The remaining patients had mainly intermediate-risk disease. The key finding was that AM was as effective as active treatment at 15 years (CSS = 96.9% in the AM-group vs. 97.8% in the RP-group and 97.1% in the EBRT-group, p=0.53), but at a cost of increased metastatic progression risk (9.4% vs. 4.7% and 5.0% respectively), as well as clinical progression at 15 years (25.9% for AM vs. 10.7% for RP/RT). Death from any cause occurred in 21.7% of the cohort, with similar numbers across treatment groups. Metastases, although rare, were more frequent than seen with comparable AS protocols [487]. A comprehensive characterisation of the ProtecT study cohort was performed after ten years, stratifying patients at baseline according to risk of progression using clinical stage, grade at diagnosis and PSA level [490]. Additionally, detailed clinico-pathological information on participants who received RP were analysed. The 15-year paper reported updated contemporary risk-stratification according to D'Amico (24.1% Intermediate risk, 9.6% high risk), CAPRA (26.4% Score 3-5, 2.5% Score 6-10) and Cambridge Prognostic Group (20.5% Group 2, 8.8% Groups 3-5). Among patients who underwent prostatectomy, 50.5% were ISUP grade group ≥2, while 28.5% had an increase in pathological stage and 32% had an increase in tumour grade. Additionally, 51% of patients who developed metastases displayed ISUP grade group 1 and 47.6% were low CAPRA risk. Over time, 61.1% of patients in the AM group received radical treatment (from 54.8% at ten years). From the ten year report the authors aimed identify prognostic markers. The results showed that treatment received, age (65–69 vs. 50–64 years), PSA, ISUP grade group at diagnosis, cT stage, risk group, number of PCa-involved biopsy cores, maximum length of tumour (median 5.0 vs. 3.0 mm), aggregate length of tumour (median 8.0 vs. 4.0 mm), and presence of perineural invasion were each associated with increased risk of disease progression (p < 0.001 for each). However, these factors could not reliably predict progression in individuals. Notably, 53% (n = 105) of patients who progressed had biopsy ISUP grade group 1 disease, although, conversely, none of the participants who received RP and subsequently progressed had pathological ISUP grade group 1 tumours. This discrepancy in progression and metastases rate between the AM arm of the ProtecT study and comparable AS protocols can, most likely, be explained by inadequate sampling by PSA testing and 10-core TRUS-guided biopsies and differences in intensity of surveillance.

It is important to note that the AM arm in ProtecT represented an intermediate approach between contemporary AS protocols and WW in terms of a monitoring strategy based almost entirely on PSA measurements alone; there was no use of MRI scan, either at recruitment or during the monitoring period, nor were there any protocol-mandated repeat prostate biopsies at regular intervals. In addition, approximately 40% of randomised patients had intermediate-risk disease (both ISUP grade group 2 and 3). Nevertheless, the ProtecT study has reinforced

the role of deferred active treatment (i.e., either AS or some form of initial AM) as a feasible alternative to active curative interventions in all patients with low-grade and low-stage disease, as well as for many patients with favourable intermediate risk disease. Beyond 15 years, no RCT-data are available, as yet, although AS is likely to give more reassurance especially in younger men, based on more accurate risk stratification at recruitment and more stringent criteria regarding follow-up, imaging, repeat biopsy and reclassification. Individual life expectancy must continuously be evaluated before considering any active treatment in low-risk patients and in those with up to ten to 15 years' individual life expectancy [490].

6.2.1.2.1 Active surveillance - inclusion criteria

Guidance regarding selection criteria for AS is limited by the lack of data from prospective RCTs. As a consequence, the Panel undertook an international collaborative study involving healthcare practitioners and patients to develop consensus statements for deferred treatment with curative intent for localised PCa, covering all domains of AS (DETECTIVE Study) [330], as well as a formal SR on the various AS protocols [491]. The criteria most often published include: ISUP grade group 1, clinical stage cT1c or cT2a, PSA < 10 ng/mL and PSA-D < 0.15 ng/mL/cc, as based on systematic biopsy schemes [487, 492]. The latter threshold remains controversial [492, 493]. These criteria were supported by the DETECTIVE study consensus. There was no agreement on the maximum number of systematic cores that can be involved with cancer or the maximum percentage core involvement (CI), although there was recognition that extensive disease on MRI should exclude men from AS, even though there is no firm definition on this, especially when targeted biopsies confirm ISUP grade group 1 [330]. The Movember consensus group, consisting of 27 healthcare professional and 12 lived experience participants from across the world, agreed that ISUP grade group and MRI were the most important criteria for determining eligibility to AS [494]. A SR and meta-analysis found three clinico-pathological variables which were significantly associated with reclassification, high PSA-D, > 2 positive cores (on systematic biopsies) and African-American descent [495]. A review on the risk of progression for African-American men on AS also indicated a potential increased risk of progression, but the association was not strong enough to discourage African-American men from undergoing AS, but thorough confirmatory testing is important [496]. In addition, a previous pathology consensus group suggested excluding men from AS when any of the following features were present: predominant ductal carcinoma (including pure IDC), cribriform histology, sarcomatoid carcinoma, small cell carcinoma, EPE or LVI in needle biopsy [497] and perineural invasion [498].

A multi-disciplinary consensus conference on germline testing has suggested a genetic implementation framework for the management of PCa [154]. Based on consensus, *BRCA2*-gene testing was recommended for AS discussions and could be performed in men with family history of prostate, breast or ovarian cancers. However, the nature of such discussions and how a positive result influences management were beyond the scope of the project. Currently, *BRCA2* mutation does not exclude a patient from AS if tumour factors are otherwise favourable. Furthermore, if included in AS programmes, patients with a known *BRCA2* mutation should be cautiously monitored until such time that more robust data are available.

6.2.1.2.2 Tissue-based prognostic biomarker testing for selection for AS

Biomarkers, including Oncotype Dx®, Prolaris®, Decipher®, PORTOS and ProMark® are promising (see Section 5.2.8.3). However, further data will be needed before such markers can be used in standard clinical practice [220].

6.2.1.2.3 Magnetic resonance imaging for selection for active surveillance

In men eligible for AS based upon systematic biopsy findings alone who did not have a pre-biopsy MRI, a re-biopsy within six to twelve months months (usually referred to as 'confirmatory biopsy') seems mandatory to exclude sampling error. A large body of literature including two RCTs and a SR, showed that adding MRI-targeted biopsy to systematic sampling at confirmatory biopsy improved detection of ISUP grade group ≥ 2 cancers and thus, patient selection for AS [121, 499-504]. Adding MRI-targeted biopsy to systematic sampling at confirmatory biopsy improved upgrade detection by increments of 0-7.9 per 100 men depending on the series [499]. In a meta-analysis of 6 studies, the rate of upgrading to ISUP grade group ≥ 2 cancer increased from 20% (95% CI: 16–25%) to 27% (95% CI: 22–34%) when MRI-targeted biopsy was added to systematic biopsy [504]. The Active Surveillance MRI Study (ASIST) randomised men on AS scheduled for confirmatory biopsy to either 12-core systematic biopsy or to MRI with targeted biopsy (when indicated), combined with systematic biopsy (up to 12 cores in total). After two years of follow-up, use of MRI before confirmatory biopsy resulted in fewer failures of surveillance (19% vs. 35%, p = 0.017) and in fewer patients progressing to ISUP grade group ≥ 2 cancer (9.9% vs. 23%, p = 0.048) [502]. However, systematic biopsy retains its additional value, which argues for a combined biopsy approach [499, 504]. The DETECTIVE study agreed that men eligible for AS after combined systematic- and MRI-targeted biopsy do not require a confirmatory biopsy, a recommendation further supported by the results of the MRIAS trial [330, 505].

If the PCa diagnosis is made on MRI-targeted biopsy alone in order to lower the risk of over-detection of insignificant (see 5.4.1 and 5.4.2.), a confirmative systematic biopsy should be performed before definite decision of AS to rule out more widespread cancer growth in the prostate [186, 189, 190].

A few studies indicate that PSMA-PET-CT or PSMA-PET-MRI may have additional value to above mentioned clinico-pathological variables for risk stratification before AS [122, 506]. However, so far, the studies are too small and the follow-up too short to draw any hard conclusions and for this modality to be recommended outside clinical trials.

6.2.1.2.4 Active surveillance management

Based on the DETECTIVE consensus study, the surveillance strategy should be based on serial DRE (at least once yearly), PSA (at least once, every six months) and repeated biopsy. It was also agreed that PSA progression or change in PSA kinetics alone should lead to reclassification only if accompanied by changes in histology on repeat biopsy [330]. The Movember consensus group stated that patients suitable for AS who suffer, or are at risk of, significant psychological distress should be offered more support, rather than active treatment. Furthermore, they made a number of recommendations that in some ways differ from the DETECTIVE consensus study, e.g. that routine DRE was not supported if MRI or other imaging was carried out routinely during AS, that if MRI and other parameters (PSA kinetics and density) are stable routine biopsy may be omitted and that change in clinical parameters should prompt MRI with possible biopsy rather than immediate biopsy [494]. The somewhat contradicting recommendations, made by these two different international consensus groups so close in time, clearly illustrate the lack of high-level evidence on how the strategy of AS should be planned and the urgent need of prospective randomised trials.

In 2016, the Prostate Cancer Radiological Estimation of Change in Sequential Evaluation (PRECISE) criteria were established to standardise the assessment of tumour progression on serial MRI [507]. Progression on MRI, or not, as defined by PRECISE criteria, is a strong predictor of histological upgrading [508, 509]. Two independent meta-analyses assessed the value of MRI progression criteria for predicting histological progression (mostly defined as progression to ISUP grade group ≥ 2). The pooled histological progression rate was 27% in both reviews. If biopsies were triggered only by MRI progression findings, approximately two thirds of the biopsies would be avoided, at the cost of missing 40% of men with histological progression. In addition, at least half of biopsied men would have had negative findings for histological progression and thus would have undergone unnecessary biopsies. If histological progression was restricted to progression to ISUP grade group > 3, approximately 30% of histological progression would be missed and approximately 80% of the biopsies performed would be unnecessary. The use of the PRECISE criteria did not seem to change these results [510, 511]. This supports maintaining protocol-mandated repeat biopsies during the course of AS.

Thus, the basis for AS protocols includes standard repeat biopsy. However, several factors have been found to be associated with low re-classification rates and long PFS: negative baseline or repeat MRI during AS [505, 512-518], low PSA-D [505, 513, 515, 518], low PSA velocity (PSAV) [519, 520] or negative biopsy (i.e., no cancer at all) at confirmatory or repeat biopsy during AS [521]. Patients with stable (PRECISE 3) on repeat MRI during AS and a low PSA-D (<0.15) have a very low rate of progression and repeat biopsy may therefore be omitted [522].

A Panel SR incorporating 263 surveillance protocols showed that 78.7% of protocols mandated per-protocol confirmatory biopsies within the first two years and that 57.7% of the protocols performed repeat biopsy at least every three years for ten years after the start of AS [491]. In another review it was concluded that a negative repeat biopsy during AS was associated with a 50% decrease in the risk of future reclassification and upgrading [523]. In a single-centre AS cohort of 514 patients who underwent at least three protocol-mandated biopsies after diagnosis (the confirmatory biopsy and at least two additional surveillance biopsies), men with one negative biopsy (i.e., no cancer at all) at confirmatory or second biopsy, or men with two consecutive negative biopsies had a lower likelihood of a positive third biopsy and significantly better 10-year treatment free survival [521]. This suggests that men with repetitive negative biopsies may pursue AS with at least less frequent untriggered biopsies.

6.2.1.2.5 Active Surveillance - change in treatment

Men may remain on AS whilst they continue to consent, have a life expectancy of > ten years and the disease remains indolent. Patient anxiety about continued surveillance occurs in around 10% of patients on AS [524] and was recognised as a valid reason for active treatment [329]. An alternative for patients suitable for continuing AS would be to offer psychological support to reduce the level of anxiety [494]. A review on patient reported factor influencing the decision making, including thirteen qualitative papers and 426 men, identified a number of factors influencing the decision making when considering AS. Among the identified factors were personal

risk assessment, influence of family and friends, beliefs about treatment as well as doctor and system factors, underscoring the importance of individualised, relevant, and clear information to support decision making [525]. A recent population-based cohort study from Sweden on regional differences in AS uptake and subsequent transition to radical treatment concluded that a regional tradition of a high uptake of AS was associated with a lower probability of transition to radical treatment, but not with AS failure [526]. These studies further emphasise the importance of thorough information and discussion with the patients on pros/cons of AS vs. active treatment already at the time of diagnosis for the patients to feel secure in their treatment choice and to avoid over-treatment.

A PSA change alone, including PSA-doubling time (PSA-DT, < 3 years) should not change management based on its weak link with grade progression [527, 528] but rather trigger further investigation. There was clear agreement in the DETECTIVE consensus meeting as well as in the Movember consensus group that a change in PSA should lead to repeat-MRI and repeat-biopsy. It was also agreed that changes on repeat MRI during AS needed a confirmatory biopsy before considering active treatment [330, 494].

The histopathology criteria required to trigger a change in management in the targeted biopsy era remain debated. MRI-targeted biopsy induces a grade shift and ISUP grade group 2–3 cancers detected by MRI-targeted biopsy have, on average, a better prognosis than those detected by systematic sampling (see Section 5.2.4.2.6.4). As an increasing number of men with favourable intermediate-risk disease are managed with AS (see section 6.2.2.1), it seems illogical to use progression to ISUP grade group 2 based on targeted biopsies as the sole criterion for reclassification. In addition, as acknowledged in the DETECTIVE consensus meeting, the number of positive cores is not an indicator of tumour volume anymore if targeted biopsies are performed [330, 529]. No agreement could be reached on the pathological criteria required to trigger a change in management during the DETECTIVE consensus meeting [330]. However, based on the findings of a SR incorporating 271 reclassification protocols, patients with low-volume ISUP grade group 2 disease at recruitment, and with increased systematic core positivity (> 3 cores involvement [> 50% per core]) on repeat systematic biopsies not using MRI, should be reclassified [491]. Furthermore, in a study from the MUSIC registry over half of men with favourable intermediate-risk prostate cancer on AS remained free of treatment five years after diagnosis [530]. Their results are in concordance with the DETECTIVE and the Movember consensus statements and indicate that most men on AS will not lose their window of cure and have similar short-term oncologic outcomes as men undergoing up-front treatment and that AS is an oncologically safe option for appropriately selected men with favourable intermediate-risk prostate cancer.

The development of other comorbidities, resulting in a life expectancy of less than ten years should merit a new discussion with the patient and may result in a decision to transfer to a WW strategy.

Table 6.2.2: Active surveillance in screening-detected prostate cancer (large cohorts with longer-term follow-up)

Studies	N	Median FU (mo)	pT3 in RP patients*	10-year OS (%)	10-year CSS (%)
Adamy, *et al.* 2011 [489]	533-1,000	48	4/24 (17%)	90	99
Godtman, *et al.* 2013 [492]	439	72	-	81	99.5
Klotz, *et al.* 2015 [493]	993	77	-	85	98.1
Tosoian, *et al.* 2020 [494]	1,818	60	-	93	99.9
Carlsson, *et al.* 2020 [495]	2,664	52	-	94	100
Total	**6,447–6,914**	**61.8**	**-**	**88.6**	**99.3**

** Patients receiving active therapy following initial active surveillance.*
CSS = cancer-specific survival; FU = follow-up; mo = months; n = number of patients; n.r. = not reported; OS = overall survival; RP = radical prostatectomy.

*6.2.2 **Radical prostatectomy***

6.2.2.1 Introduction

The goal of RP by any approach is the eradication of cancer while, whenever possible, preserving pelvic organ function [531]. The procedure involves removing the entire prostate with its capsule intact and SVs, followed by vesico-urethral anastomosis. Surgical approaches have expanded from perineal and retropubic open approaches to laparoscopic and robotic-assisted techniques; anastomoses have evolved from Vest approximation sutures to continuous suture watertight anastomoses under direct vision and mapping of the anatomy of the dorsal venous complex (DVC) and cavernous nerves has led to excellent visualisation and

potential for preservation of erectile function [532]. The main results from multi-centre RCTs involving RP are summarised in Table 6.1.3.

Table 6.2.3: Oncological results of radical prostatectomy in organ-confined disease in RCTs

Study	Acronym	Population	Treatment period	Median FU (mo)	Risk category	CSS (%)
Bill-Axelson, *et al.* 2018 [481]	SPCG-4	Pre-PSA era	1989-1999	283	Low risk and intermediate risk	80.4 (at 23 yr.)
Wilt, *et al.* 2017 [482]	PIVOT	Early years of PSA testing	1994-2002	152	Low risk and intermediate risk	95.9 91.5 (at 19.5 yr.)
Hamdy, *et al.* 2023 [474]	ProtecT	Screened population	1999-2009	180	Mainly low- and intermediate risk	97 (at 15 yr.)

CSS = cancer-specific survival; FU = follow-up; mo = months; PSA = prostate-specific antigen; yr. = year.

6.2.2.2 Pre-operative preparation

6.2.2.2.1 Pre-operative patient education

As before any surgery appropriate education and patient consent is mandatory prior to RP. Peri-operative education has been shown to improve long-term patient satisfaction following RP [533]. Augmentation of standard verbal and written educational materials such as use of interactive multimedia tools [534, 535] and pre-operative patient-specific 3D printed prostate models has been shown to improve patient understanding and satisfaction and should be considered to optimise patient-centred care [536].

6.2.2.3 Surgical techniques

6.2.2.3.1 Pelvic lymph node dissection

A SR has demonstrated that performing PLND during RP failed to improve oncological outcomes, including survival [536]. Moreover, two RCTs have failed to show a benefit of an extended approach vs. a limited PLND on early oncologic outcomes [537, 538].

Extended PLND 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, the majority of patients are correctly staged [539] and as such, ePLND provides accurate information for staging and prognosis [540].

6.2.2.3.2 Lymph-node-positive patients during radical prostatectomy

Although no RCTs are available, data from prospective cohort studies comparing survival of pN+ patients (as defined following pathological examination after RP) support that RP may have a survival benefit over abandonment of RP in node-positive cases [541]. As a consequence, there is no role for performing frozen section of suspicious LNs.

6.2.2.3.3 Sentinel node biopsy analysis

The rationale for a sentinel node biopsy (SNB) is based on the concept that a sentinel node is the first to be involved by migrating tumour cells. Therefore, when this node is negative it is possible to avoid an ePLND [542]. Intraprostatic injections of indocyanine green (ICG) have been used to visualise prostate-related LNs for SNB. In a randomised comparison, Harke *et al.*, found more cancer-containing LNs in men who underwent a PLND guided by ICG but no difference in BCR at 22.9-month follow-up [543]. A SR of 21 studies showed a sensitivity of 95.2% and NPV of 98.0% for SNB in detecting men with metastases at ePLND [544]. However, this review was hampered by widespread heterogeneity of both definitions and how SNB is performed. This prompted the development of an expert consensus report to guide further research [542].

The prospective SENTINELLE study investigated the diagnostic accuracy of sentinel lymph node biopsy-guided lymph node dissection compared to extended pelvic LN dissection in patients with intermediate- or high-risk prostate cancer. Sensitivity, specificity, NPV, and positive predictive value of SNB method in detecting patients with at least one LN metastasis were 95.4% (95% CI, 75.1-99.7), 100% (95% CI, 96.6-100), 99.2% (95% CI, 95.5-99.9), and 100% (95% CI, 80.7-100), respectively [545].

6.2.2.3.4 Prostatic anterior fat pad dissection and histologic analysis

Several multi-centre and large single-centre series have shown the presence of lymphoid tissue within the fat pad anterior to the endopelvic fascia; the prostatic anterior fat pad (PAFP) [546-552]. This lymphoid tissue is present in 5.5–10.6% of cases and contains metastatic PCa in up to 1.3% of intermediate- and high-risk patients.

When positive, the PAFP is often the only site of LN metastasis. The PAFP is therefore a rare but recognised route of spread of disease. The PAFP is always removed at RP for exposure of the endopelvic fascia and should be sent for histologic analysis as per all removed tissue.

6.2.2.3.5 Management of the dorsal venous complex

Since the description of the anatomical open RP by Walsh and Donker in the 1980s, various methods of controlling bleeding from the DVC have been proposed to optimise visualisation [553]. In the open setting, blood loss and transfusion rates have been found to be significantly reduced when ligating the DVC prior to transection [554]. However, concerns have been raised regarding the effect of prior DVC ligation on apical margin positivity and continence recovery due to the proximity of the DVC to both the prostatic apex and the urethral sphincter muscle fibres. In the robotic-assisted laparoscopic technique, due to the increased pressure of pneumoperitoneum, whether prior DVC ligation was used or not, blood loss was not found to be significantly different in one study [555]. In another study, mean blood loss was significantly less with prior DVC ligation (184 vs. 176 mL, $p = 0.033$), however it is debatable whether this was clinically significant [556]. The positive apical margin rate was not different, however, the latter study showed earlier return to full continence at five months post-operatively in the no prior DVC ligation group (61% vs. 40%, $p < 0.01$).

Ligation of the DVC can be performed with standard suture or using a vascular stapler. One study found significantly reduced blood loss (494 mL vs. 288 mL) and improved apical margin status (13% vs. 2%) when using the stapler [557].

Given the relatively small differences in outcomes, the surgeon's choice to ligate prior to transection or not, or whether to use sutures or a stapler, will depend on their familiarity with the technique and the equipment available.

6.2.2.3.6 Nerve-sparing surgery

During prostatectomy, preservation of the neurovascular bundles (NVB) with parasympathetic nerve branches of the pelvic plexus can spare erectile function [558, 559].

Extra-, inter-, and intra-fascial dissection planes can be planned, with those closer to the prostate and performed bilaterally associated with superior (early) functional outcomes [560-563]. Furthermore, many different techniques are propagated such as retrograde approach after anterior release (vs. antegrade), and athermal and traction-free handling of bundles [564-566]. Nerve-sparing (NS) surgery may be performed using clips or low bipolar energy without clear benefit favouring one technique over another regarding functional outcomes [567].

A 2021 large retrospective study of high-risk patients also found that NS did not affect BCR, risk of metastasis or of death [568]. Notably, clinical and pathological stage T3 and ISUP grade group 5 did not impact these oncological outcomes. However, as a retrospective study, it was subject to selection bias, whereby patients with unfavourable characteristics were more likely to have undergone non-nerve-sparing surgery.

A 2021 SR of 19 studies analysing the parameters used for selection of NS found that individual clinical and radiological factors were poor at predicting EPE, and consequently, the appropriateness of NS. However, nomograms that incorporated mpMRI performed better. As with all nomograms, the question remains as to where to set the cut-off point [569].

A 2022 SR of 18 comparative studies (no RCTs) of NS vs. non-nerve-sparing RP showed a RR of side-specific positive margins of 1.5, but none of them included patients with high-risk PCa [570]. There was no effect seen of NS on BCR. However, follow-up was short, and studies were subject to selection bias with mainly low-risk patients. For those patients with high-risk PCa, side-specific NS was avoided if disease was palpable or EPE was present on MRI. Indeed, a 2019 SR showed that MRI affected the decision to perform NS or not in 35% of cases without any negative impact on surgical margin rate [571] (See Section 5.3.2).

Although age and pre-operative function may remain the most important predictors for post-operative erectile function, NS has also been associated with improved continence outcomes and may therefore still be relevant for men with poor erectile function [572, 573]. The association with continence may be mainly due to the dissection technique used during NS surgery, and not due to the preservation of the NVB themselves [572].

In summary, the quality of data is not adequate to permit a strong recommendation in favour of NS or non-nerve-sparing, but pre-operative risk factors for side-specific EPE such as PSA, PSA density, clinical stage, ISUP grade group, and PIRADS score, EPE and capsule contact length on MRI, should be taken into account.

6.2.2.3.7 Removal of seminal vesicles

The more aggressive forms of PCa may spread directly into the SVs. For oncological clearance, the SVs have traditionally been removed intact with the prostate specimen [574]. However, in some patients the tips of the SVs can be challenging to dissect free. Furthermore, the cavernous nerves run past the SV tips such that indiscriminate dissection of the SV tips could potentially lead to ED [575]. However, a RCT comparing nerve-sparing RP with and without a SV-sparing approach found no difference in margin status, PSA recurrence, continence or erectile function outcomes. Whilst complete SV removal should be the default, preservation of the SV tips may be considered in cases of low risk of involvement.

6.2.2.3.8 Techniques of vesico-urethral anastomosis

Following prostate removal, the bladder neck is anastomosed to the membranous urethra. The objective is to create a precisely aligned, watertight, tension-free, and stricture-free anastomosis that preserves the integrity of the intrinsic sphincter mechanism. Several methods have been described, based on the direct or indirect approach, the type of suture (i.e. barbed vs. non-barbed/monofilament), and variation in suturing technique (e.g., continuous vs. interrupted, or single-needle vs. double-needle running suture). The direct vesico-urethral anastomosis, which involves the construction of a primary end-to-end inter-mucosal anastomosis of the bladder neck to the membranous urethra by using 6 interrupted sutures placed circumferentially, has become the standard method of reconstruction for open RP [576].

The development of laparoscopic- and robotic-assisted techniques to perform RP have facilitated the introduction of new suturing techniques for the anastomosis. A SR and meta-analysis compared unidirectional barbed suture vs. conventional non-barbed suture for vesico-urethral anastomosis during robotic-assisted laparoscopic prostatectomy (RALP) [577]. The review included 3 RCTs and found significantly reduced anastomosis time, operative time and posterior reconstruction time in favour of the unidirectional barbed suture technique, but there were no differences in post-operative leak rate, length of catheterisation and continence rate. However, no definitive conclusions could be drawn due to the relatively low quality of the data. In regard to suturing technique, a SR and meta-analysis compared continuous vs. interrupted suturing for vesico-urethral anastomosis during RP [578]. The study included only one RCT with 60 patients [579]. Although the review found slight advantages for continuous suturing over interrupted suturing in terms of catheterisation time, anastomosis time and rate of extravasation, the overall quality of evidence was low and no clear recommendations were possible. A RCT [580] compared the technique of suturing using a single absorbable running suture vs. a double-needle single-knot running suture (i.e. Van Velthoven technique) in laparoscopic RP [581]. The study found slightly reduced anastomosis time with the single running suture technique, but anastomotic leak, stricture, and continence rates were similar.

Overall, although there are a variety of approaches, methods, and techniques for performing the vesico-urethral anastomosis, no clear recommendations are possible due to the lack of high-certainty evidence. In practice, the chosen method should be based on surgeon experience and individual preference [576-581].

6.2.2.3.9 Bladder neck management

Bladder neck mucosal eversion

Some surgeons perform mucosal eversion of the bladder neck as its own step in open RP with the aim of securing a mucosa-to-mucosa vesico-urethral anastomosis and avoiding anastomotic stricture. Whilst bringing bladder and urethral mucosa together by the everted bladder mucosa covering the bladder muscle layer, this step may actually delay healing of the muscle layers. An alternative is to simply ensure bladder mucosa is included in the full thickness anastomotic sutures. A non-randomised study of 211 patients with and without bladder neck mucosal eversion showed no significant difference in anastomotic stricture rate [582]. The strongest predictor of anastomotic stricture in RP is current cigarette smoking [583], but it is also 2.2 higher in open RP than RARP [584].

Bladder neck preservation

Whilst the majority of urinary continence is maintained by the external urethral sphincter at the membranous urethra (see below), a minor component is contributed by the internal lissosphincter at the bladder neck [585]. Preservation of the bladder neck has therefore been proposed to improve continence recovery post-RP. A RCT assessing continence recovery at twelve months and four years showed improved objective and subjective urinary continence in both the short- and long term without any adverse effect on oncological outcome [586].

These findings were confirmed by a SR [587]. However, concern remains regarding margin status for cancers located at the prostate base.

A SR addressing site-specific margin status found a mean base-specific positive margin rate of 4.9% with bladder neck preservation vs. only 1.9% without [585]. This study was inconclusive, but it would be sensible to exercise caution when considering bladder neck preservation if significant cancer is known to be at the prostate base. Bladder neck preservation should be performed routinely when the cancer is distant from the base. However, bladder neck preservation cannot be performed in the presence of a large median lobe or a previous transurethral resection of the prostate (TURP) [588].

6.2.2.3.10 Urethral length preservation

The membranous urethra sits immediately distal to the prostatic apex and is chiefly responsible, along with its surrounding pelvic floor support structures, for urinary continence. It consists of the external rhabdosphincter which surrounds an inner layer of smooth muscle. Using pre-operative MRI, the length of membranous urethra has been shown to vary widely.

Systematic reviews and meta-analyses found that every extra millimetre of membranous urethral length seen on MRI pre-operatively improves early return to continence post-RP [589-591]. A greater membranous urethral length as measured on preoperative MRI was an independent prognostic factor for return to urinary continence within one month after RP and remained prognostic at twelve months [591]. Therefore, it is likely that preservation of as much urethral length as possible during RP will maximise the chance of early return to continence. It may also be useful to measure urethral length pre-operatively on MRI to facilitate counselling of patients on their relative likelihood of early post-operative continence [592].

6.2.2.3.11 Cystography prior to catheter removal

Cystography may be used prior to catheter removal to check for a substantial anastomotic leak. If such a leak is found, catheter removal may then be deferred to allow further healing and sealing of the anastomosis. However, small comparative studies suggest that a cystogram to assess anastomotic leakage is not indicated as SOC before catheter removal eight to ten days after surgery [593]. If a cystogram is used, men with LUTS, large prostates, previous TURP or bladder neck reconstruction, may benefit as these factors have been associated with leakage [594, 595]. Contrast-enhanced transrectal US is an alternative [596].

6.2.2.3.12 Urinary catheter

A urinary catheter is routinely placed during RP to enable bladder rest and drainage of urine while the vesicourethral anastomosis heals. Compared to a traditional catheter duration of around one week, some centres remove the transurethral catheter early (post-operative day 2–3), usually after thorough anastomosis with posterior reconstruction or in patients selected peri-operatively on the basis of anastomosis quality [597-600]. No higher complication rates were found. Although shorter catheterisation has been associated with more favourable short-term functional outcomes, no differences in long-term function were found [601]. One RCT has shown no difference in rate of UTI following indwelling catheter (IDC) removal whether prophylactic ciprofloxacin was given prior to IDC removal or not, suggesting antibiotics should not be given at catheter removal [602].

As an alternative to transurethral catheterisation, suprapubic catheter insertion during RP has been suggested. Some reports suggest less bother regarding post-operative hygiene and pain [603-607], while others did not find any differences [608, 609]. No impact on long-term functional outcomes were seen.

6.2.2.3.13 Use of a pelvic drain

A pelvic drain has traditionally been used in RP for potential drainage of urine leaking from the vesico-urethral anastomosis, blood, or lymphatic fluid when a PLND has been performed. Two RCTs in the robotic-assisted laparoscopic setting have been performed [610, 611]. Patients with urine leak at intra-operative anastomosis watertight testing were excluded. Both trials showed non-inferiority in complication rates when no drain was used. When the anastomosis is found to be watertight intra-operatively, it is reasonable to avoid inserting a pelvic drain. There is no evidence to guide usage of a pelvic drain in PLND.

6.2.2.4 Acute and chronic complications of radical prostatectomy

Post-operative incontinence and ED are common problems following surgery for PCa. A key consideration is whether these problems are reduced by using newer techniques such as RALP. Systematic reviews have documented complication rates after RALP [612-616], and can be compared with contemporaneous reports after radical retropubic prostatectomy (RRP) [617]. A prospective controlled non-RCT of patients undergoing RP in 14 centres using RALP or RRP showed that twelve months after RALP, 21.3% of patients were incontinent, as were 20.2% after RRP (adjusted OR: 1.08, 95% CI: 0.87–1.34) [618]. 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) [618].

A SR and meta-analysis of unplanned hospital visits and re-admissions post-RP analysed 60 studies with over 400,000 patients over a 20-year period up to 2020. It found an emergency room visit rate of 12% and a hospital re-admission rate of 4% at 30 days post-operatively [619].

A RCT comparing RALP and RRP reported outcomes at 12 weeks in 326 patients and functional outcomes at two years [620]. Urinary function scores did not differ significantly between RRP vs. RALP at 6 and 12 weeks post-surgery (74–50 vs. 71–10, p = 0.09; 83–80 vs. 82–50, p = 0.48), with comparable outcomes for sexual function scores (30–70 vs. 32–70, p = 0.45; 35–00 vs. 38–90, p = 0.18). In the RRP group 14 (9%) patients had post-operative complications vs. 6 (4%) in the RALP group. The intra- and peri-operative complications of RRP and RALP are listed in Table 6.1.4. Table 6.1.5 lists the Clavien-Dindo definition of surgical complications. The early use of phosphodiesterase-5 (PDE5) inhibitors in penile rehabilitation remains controversial resulting in a lack of clear recommendations (see Section 8.3.2.1).

Table 6.2.4: Intra-and peri-operative complications of retropubic RP, laparoscopic RP and RALP (adapted from [612])

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-Dindo I	2.1	4.1	4.2
Clavien-Dindo II	3.9	7.2	17.5
Clavien-Dindo IIIa	0.5	2.3	1.8
Clavien-Dindo IIIb	0.9	3.6	2.5
Clavien-Dindo IVa	0.6	0.8	2.1
Clavien-Dindo V	< 0.1	0.2	0.2

RALP = robot-assisted laparoscopic prostatectomy; RP = radical prostatectomy; RRP = radical retropubic prostatectomy.

Table 6.2.5: Clavien-Dindo grading of surgical complications [621]

Grade	**Definition**
I	Any deviation from the normal post-operative course not requiring surgical, endoscopic or radiological intervention. This includes the need for certain drugs (e.g. antiemetics, antipyretics, analgesics, diuretics and electrolytes), treatment with physiotherapy and wound infections that are opened at the bedside
II	Complications requiring drug treatments other than those allowed for Grade I complications; this includes blood transfusion and total parenteral nutrition (TPN)
IIIa	Complications requiring surgical, endoscopic or radiological intervention - intervention not under general anaesthetic
IIIb	Complications requiring surgical, endoscopic or radiological intervention - intervention under general anaesthetic
IVa	Life-threatening complications; this includes central nervous system (CNS) complications (e.g. brain haemorrhage, ischaemic stroke, subarachnoid haemorrhage) which require intensive care, but excludes transient ischaemic attacks (TIAs) - single-organ dysfunction (including dialysis)
IVb	Life-threatening complications; this includes CNS complications (e.g. brain haemorrhage, ischaemic stroke, subarachnoid haemorrhage) which require intensive care, but excludes transient ischaemic attacks (TIAs) - multi-organ dysfunction
V	Death of the patient

6.2.2.4.1 Effect of anterior and posterior reconstruction on continence

Preservation of integrity of the external urethral sphincter is critical for continence post-RP. Less clear is the effect of reconstruction of surrounding support structures to return to continence. Several small RCTs have been conducted, however, pooling analyses is hampered by variation in the definitions of incontinence and surgical approach, such as open vs. robotic and intra-peritoneal vs. extra-peritoneal. In addition, techniques used to perform both anterior suspension or reconstruction and posterior reconstruction are varied. For example, anterior suspension is performed either through periosteum of the pubis or the combination of ligated DVC and puboprostatic ligaments (PPL). Posterior reconstruction from rhabdosphincter is described to either Denonvilliers fascia posterior to bladder or to posterior bladder wall itself.

Two trials assessing posterior reconstruction in RALRP found no significant improvement in return to continence [622, 623]. A third trial using posterior bladder wall for reconstruction showed only an earlier return to 1 pad per day (median 18 vs. 30 days, p = 0.024) [624]. When combining both anterior and posterior reconstruction, where for anterior reconstruction the PPL were sutured to the anterior bladder neck, another RCT found no improvement compared to a standard anastomosis with no reconstruction [625].

Four RCTs including anterior suspension have also shown conflicting results. Anterior suspension alone through the pubic periosteum, in the setting of extra-peritoneal RALRP, showed no advantage [626]. However, when combined with posterior reconstruction in RRP, one RCT showed significant improvement in return to continence at one month (7.1% vs. 26.5%, p = 0.047) and three months (15.4% vs. 45.2%, p = 0.016), but not at six months (57.9% vs. 65.4%, p = 0.609) [627]. Another anterior plus posterior reconstruction RCT using the Advanced Reconstruction of VesicoUrethral Support (ARVUS) technique and the strict definition of continence of 'no pads', showed statistically significant improvement in continence at 2 weeks (43.8% vs. 11.8%), 4 weeks (62.5% vs. 14.7%), 8 weeks (68.8% vs. 20.6%), six months (75% vs. 44.1%) and twelve months (86.7% vs. 61.3%), when compared to standard posterior Rocco reconstruction [628]. Anterior suspension alone through the DVC and PPL combined without posterior construction in the setting of RRP has shown improvement in continence at one month (20% vs. 53%, p = 0.029), three months (47% vs. 73%, p = 0.034) and six months (83% vs. 100%, p = 0.02), but not at twelve months (97% vs. 100%, p = 0.313) [629]. Together, these results suggest a possible earlier return to continence, but no long-term difference.

As there is conflicting evidence on the effect of anterior and/or posterior reconstruction on return to continence post-RP, no recommendations can be made. However, no studies showed an increase in adverse oncologic outcome or complications with reconstruction.

6.2.2.4.2 Deep venous thrombosis prophylaxis

For EAU Guidelines recommendations on post-RP deep venous thrombosis prophylaxis, please see the Thromboprophylaxis Guidelines Section 3.1.6 [630]. However, these recommendations should be adapted based on national recommendations, when available.

6.2.2.4.3 Complications of extended pelvic lymph node dissection

Extended PLND increases morbidity in the treatment of PCa [540]. Overall complication rates of 19.8% vs. 8.2% were noted for ePLND vs. limited PLND, respectively, with lymphoceles (10.3% vs. 4.6%) being the most common adverse event (AE). Other authors have reported lower complication rates [631]. Briganti *et al.*, [632] also showed more complications after extended compared to limited PLND. Twenty percent of men suffer a complication of some sort after ePLND. Thromboembolic events occur in less than 1% of cases overall, but the RR of DVT and PE associated with PLND has been found to be 7.8 and 6.3, respectively [633].

*6.2.3 **Radiotherapy***

Intensity-modulated RT (IMRT) or volumetric modulated arc therapy (VMAT) with image-guided RT (IGRT) is currently widely recognised as the standard treatment approach for EBRT.

6.2.3.1 External beam radiation therapy

6.2.3.1.1 Technical aspects

Intensity-modulated RT and VMAT employ dynamic multi-leaf collimators, which automatically and continuously adapt to the contours of the target volume seen by each beam. Viani *et al.*, show significantly reduced acute and late grade ≥ 2 genito-urinary (GU) and gastro-intestinal (GI) toxicity in favour of IMRT, while BCR-free rates did not differ significantly when comparing IMRT with three-dimensional conformal RT (3D-CRT) in a RCT comprising 215 patients [634]. A meta-analysis by Yu *et al.*, (23 studies, 9,556 patients) concluded that IMRT significantly decreases the occurrence of grade 2–4 acute GI toxicity, late GI toxicity and late rectal bleeding, and achieves better PSA relapse-free survival in comparison with 3D-CRT. Intensity-modulated EBRT and 3D-CRT show comparable acute rectal toxicity, late GU toxicity and OS, while IMRT slightly increases the morbidity of

acute GU toxicity [635]. Zapatero *et al.*, found, based on 733 consecutive patients (295 IMRT vs. 438 3D-CRT), that compared with 3D-CRT, high-dose IMRT/IGRT is associated with a lower rate of late urinary complications despite a higher radiation dose [636]. In conclusion, IMRT plus IGRT remain the SOC for the treatment of PCa.

The advantage of VMAT over IMRT is shorter treatment times, generally two to three minutes in total. Both techniques allow for a more complex distribution of the dose to be delivered and provide concave isodose curves, which are particularly useful as a means of sparing the rectum. Radiotherapy treatment planning for IMRT and VMAT differs from that used in conventional EBRT, requiring a computer system capable of 'inverse planning' and the appropriate physics expertise. Treatment plans must conform to pre-specified dose constraints to critical organs at risk of normal tissue damage and a formal quality assurance process should be routine.

With dose escalation using IMRT/VMAT, organ movement becomes a critical issue in terms of both tumour control and treatment toxicity. Techniques will therefore combine IMRT/VMAT with some form of IGRT (usually gold marker or cone-beam CT), in which organ movement can be visualised and corrected for in real time, although the optimum means (number of applications per week) of achieving this is still unclear [637, 638]. Tomotherapy is another technique for the delivery of IMRT, using 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.

The use of MR-guided adapted RT is still investigational [639]. Planning studies confirm that MR-based adaptive RT significantly reduces doses to organs at risk (OAR) and this may translate into clinical benefit [640]. Although the rates of acute GI- and GU toxicity appear low, mostly on the basis of patients treated with stereotactic RT [641], follow-up is too short for definitive conclusions [639]. The daily fraction time of up to 45 minutes [639, 641], the heavy MR-workflow and the limited field size (rendering most pelvic fields too large) make its implementation not yet a routine [639]. A prospective single center RCT, the MIRAGE trial (CT-guided Stereotactic Body Radiation Therapy and MRI-guided Stereotactic Body Radiation Therapy for Prostate Cancer) demonstrates reduced acute GU and GI toxicity with MRI-guided SBRT and margin reduction from 4mm to 2mm [642]. The impact on long term toxicity, biochemical control and cost effectiveness remains undefined.

6.2.3.1.2 Dose escalation

Local control is a critical issue for the outcome of RT of PCa. It has been shown that local failure due to insufficient total dose is prognostic for death from PCa as a second wave of metastases is seen five to ten years later on [643]. Several RCTs have shown that dose escalation (range 74–80 Gy) has a significant impact on 10-year biochemical relapse as well as metastases and disease-specific mortality [644-651]. These trials have generally included patients from several risk groups, and the use of neoadjuvant/adjuvant HT has varied (see Table 6.1.6). The best evidence of an OS benefit in patients with intermediate- or high-risk PCa, but not with low-risk PCa, derives from a non-randomised but well conducted propensity-matched retrospective analysis of the U.S. National Cancer Database by Kalbasi *et al.*, including a total of 42,481 patients [652]. If IMRT/VMAT and IGRT are used for dose escalation, rates of severe late side effects (> grade 3) for the rectum are 2–4% and for the GU tract 2–6% [646, 653].

The concept of a focal boost to the dominant intraprostatic lesion (DIL) visible on MRI rather than global prostate dose escalation has been successfully validated in a RCT of 571 intermediate- and high-risk patients [653]. Patients were randomised between 77 Gy in 35 fractions of 2.2 Gy and the same dose plus a focal boost up to 18 Gy. Additional ADT was given to 65% of patients in both arms. However, the duration of the ADT was not reported. With a median follow-up of 72 months there was a moderate improvement of biochemical PFS (BPFS) (primary endpoint). In addition, focal boosting decreased local failure (HR: 0.33) and increased the rate of regional + distant MFS (HR: 0.58) [654]. No significant difference for late GU- or GI toxicity grade ≥ 2 (23% and 12% vs. 28% and 13%) was documented. For grade ≥ 3 GU-toxicity these numbers were 3.5% and 5.6% ($p > 0.05$). However, longer follow-up is needed to assess late GU-toxicity [654]. Of note, there was a clear decrease in biochemical failure with increasing boost dose, individually given up to 18 Gy. Systematic review of MRI-defined DIL focal boost studies using standard fractionation shows good tolerability and improved BPFS [655]. Its role when using hypofractionation and ultra-hypofractionation is under investigation.

Table 6.2.6: Randomised trials of dose escalation in localised PCa

Trial	n	PCa condition	Radiotherapy Dose	Follow-up (median)	Outcome	Results
MD Anderson study 2011 [651]	301	T1-T3, N0, M0, PSA ≤ 10 ng/mL PSA 10-20 ng/mL PSA > 20 ng/mL	70 vs.78 Gy	15 yr.	DM, DSM, FFF	All patients: 18.9% FFF at 70 Gy 12% FFF at 78 Gy (p = 0.042) 3.4% DM at 70 Gy 1.1% DM at 78 Gy (p = 0.018) 6.2% DSM at 70 Gy 3.2% DSM at 78 Gy (p = 0.043) No difference in OS (p > 0.05)
PROG 95-09 2010 [645]	393	T1b-T2b PSA ≤ 15 ng/mL 75% low-risk pts. Low-risk: T1-2a, PSA < 10 mg/mL, GS ≤ 6 Interm-risk: PSA 10-15 ng/mL or GS 7 or T2b High-risk: GS 8-10	70.2 vs.79.2 Gy including proton boost 19.8 vs. 28.8 Gy	8.9 yr.	10-yr. ASTRO BCF	All patients: 32% BF at 70.2 Gy 17% BF at 79.2 Gy (p < 0.0001) Low-risk patients: 28% BF at 70.2 Gy 7% BF at 79.2 Gy (p < 0.0001
MRC RT01 2014 [650]	843	T1b-T3a, N0, M0 PSA < 50 ng/mL neoadjuvant HT	64 vs. 74 Gy	10 yr.	BFS, OS	43% BFS at 64 Gy 55% BFS at 74 Gy (p = 0.0003) 71% OS both groups (p = 0.96)
Dutch randomised phase III trial 2014 [649]	664	T1b-T4 143 pts. with (neo) adjuvant HT	68 vs. 78 Gy	110 mo.	Freedom biochemical (Phoenix) and/or clinical failure at 10 yr.	43% FFF at 68 Gy 49% FFF at 78 Gy (p = 0.045)
GETUG 06 2011 [648]	306	T1b-T3a, N0, M0 PSA < 50 ng/mL	70 vs. 80 Gy	61 mo.	BCF (ASTRO)	39% BF at 70 Gy 28% BF at 80 Gy
RTOG 0126 2018 [644]	1,532	T1b-T2b ISUP grade group 1 + PSA 10-20 ng/mL or ISUP grade group 2/3 + PSA < 15 ng/mL	70.2 vs. 79.2 Gy	100 mo.	OS, DM, BCF (ASTRO)	75% OS at 70.2 Gy 76% OS at 79.2 Gy 6% DM at 70.2 Gy 4% DM at 79.2 Gy (p = 0.05) 47% BCF at 70.2 Gy 31% BCF at 79.2 Gy (p < 0.001; Phoenix, p < 0.001)

FLAME Trial [653, 654]	571	EAU risk classification: Intermediate risk (15%) High risk (84%)	77 Gy (35 Fx. 2.2 Gy) vs. 77 Gy (35 Fx.) + focal boost (up to 18 Gy) ADT (65% both arms – duration unknown)	72 mo. (median)	BFS (5 yr.) DSM (5 yr.)	BFS: 92% at 77 Gy + boost 85% at 77 Gy (p < 0.001, HR: 0.45) DSM: p= 0.49 Focal boost in favour of: Local control (HR: 0.33) Distant MFS (HR: 0.58)

ADT = androgen-deprivation therapy; BF = biochemical failure; BFS = biochemical progression-free survival; DM = distant metastases; DSM = 50disease specific mortality; FFF = freedom from biochemical or clinical failure; Fx = fractions; GS = Gleason score; HT = hormone therapy; ISUP = International Society of Urological Pathology; MFS = metastasis-free survival; mo. = months; n = number of patients; OS = overall survival; PSA = prostate-specific antigen; yr. = year.

6.2.3.1.3 Hypofractionation

Fractionated RT utilises differences in the DNA repair capacity of normal and tumour tissue and slowly proliferating cells are very sensitive to an increased dose per fraction [656]. A meta-analysis of 25 studies including > 14,000 patients concluded that since PCa has a slow proliferation rate, hypofractionated RT could be more effective than conventional fractions of 1.8–2 Gy [657]. Hypofractionation (HFX) has the added advantage of being more convenient for the patient at lower cost.

Moderate HFX is defined as RT with 2.5–3.4 Gy/fx. Several studies report on moderate HFX applied in various techniques also including HT in part [658-665]. A SR concluded that studies on moderate HFX (2.5–3.4 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 [664]. These results were confirmed by a Cochrane review on moderate HFX for clinically localised PCa [666]. Eleven studies were included (n = 8,278) with a median follow-up of 72 months showing little or no difference in PCa-specific survival (HR: 1.00). Based on 4 studies (n = 3,848), HFX probably makes little or no difference to late radiation GU toxicity (RR: 1.05) or GI toxicity (RR: 1.1), but this conclusion is based on relatively short follow-up, and ten to 15-year data will be required to confirm these findings.

Moderate HFX should only be done by experienced teams using high-quality EBRT using IGRT and IMRT/VMAT and published phase III protocols should be adhered to (Table 6.1.7).

Table 6.2.7: Major phase III randomised trials of moderate hypofractionation for primary treatment

Study/ Author	n	Risk, ISUP grade, or NCCN	ADT	RT Regimen	BED, Gy	Median FU, mo	Outcome
Lee, *et al.* 2016 [660]	550 542	low risk	None	70 Gy/28 fx 73.8 Gy/41 fx	80 69.6	70	**5 yr. DFS 86.3%** (n.s.) **5 yr. DFS 85.3%**
Dearnaley, *et al.* CHHiP 2016 [661]	1,077/19 fx 1,074/20 fx 1,065/37 fx	15% low 73% intermediate 12% high	3-6 mo. before and during EBRT	57 Gy/19 fx 60 Gy/20 fx 74 Gy/37 fx	73.3 77.1 74	62	**5 yr. BCDF 85.9% (19 fx) 90.6% (20 fx) 88.3% (37 fx)**
De Vries, *et al.*, 2020 [667]	403 392	30% ISUP grade 1 45% ISUP grade 2-3, 25% ISUP grade 4-5	None	64.6 Gy/19 fx 78 Gy/39 fx	90.4 78	89	**8-yr. OS 80.8% vs. 77.6%** (p = 0.17) **8 yr. TF 24.4% vs. 26.3%**

Catton, *et al.* 2017 [663]	608	intermediate risk 53% T1c 46% T2a-c	None	60 Gy/20 fx	77.1	72	**5 yr. BCDF both arms 85%** HR: 0.96 (n.s)
	598	9% ISUP grade 1 63% ISUP grade 2 28% ISUP grade 3		78 Gy/39 fx	78		

ADT = androgen deprivation therapy; BCDF = biochemical or clinical disease failure; BED = biologically equivalent dose, calculated to be equivalent in 2 Gy fractions using an α/ß of 1.5 Gy; DFS = diseasefree survival; EBRT = external beam radiotherapy; FU = follow-up; fx = fractions; HR = hazard ratio; ISUP = International Society of Urological Pathology; mo. = month; n = number of patients; NCCN = National Comprehensive Cancer Network; n.s. = not significant; TF = treatment failure; yr. = year.

Ultra-HFX has been defined as RT with > 3.4 Gy per fraction [665]. It requires IGRT and (ideally) stereotactic body RT (SBRT). Table 6.1.8 provides an overview of selected studies investigating its role in treating predominantly intermediate risk localised disease. Short-term biochemical control (5-years) is comparable to conventional fractionation. However, there are concerns about high-grade GU and rectal toxicity and full long-term side effects may not yet be known [664, 668]. In the HYPO-RT-PC randomised trial by Widmark et al., (n = 1,200), no difference in failure-free survival was seen for conventional or ultra-HFX but acute grade ≥ 2 GU toxicity was 23% vs. 28% (p = 0.057), favouring conventional fractionation. There were no significant differences in long-term toxicity [668]. A SR by Jackson et al., included 38 studies with 6,116 patients who received RT with < 10 fractions and ≥ 5 Gy per fraction. Five and seven-year biochemical recurrence-free survival (BRFS) rates were 95.3% and 93.7%, respectively, and estimated late grade ≥ 3 GU and GI toxicity rates were 2.0% and 1.1%, respectively [669]. The authors conclude that there is sufficient evidence to support SBRT as a standard treatment option for localised PCa, even though the median follow-up in this review was only 39 months and it included at least one trial (HYPO-RT-PC) which used 3D-CRT in 80% and IMRT/VMAT in the remainder for ultra-HFX. In their review on SBRT, Cushman et al., evaluated 14 trials, including 2,038 patients and concluded that despite a lack of long-term follow-up and the heterogeneity of the available evidence, prostate SBRT affords appropriate biochemical control with few high-grade toxicities [670]. In the Intensity-modulated fractionated RT vs. stereotactic body RT for PCa (PACE-B) trial, acute grade ≥ 2 GU or GI toxicities did not differ significantly between conventional fractionation and ultra- HFX [671]. At two years, treatment was well tolerated in both arms with no differences in RTOG ≥ Grade 2 GU or GI toxicities, but clinician scoring of urinary toxicity using CTCAE and patient reported Expanded Prostate Cancer Index Composite (EPIC)-26 urinary bother scores were both higher in the SBRT arm suggesting SBRT may increase moderate but not severe urinary symptoms post-teatment [672]. Adopting planning dose constraints to the penile bulb might minimise ED, especially in younger patients (Table 6.1.8) [673].

First results of a small (n = 30) randomised phase-II trial in intermediate-risk PCa of 'ultra-high single dose RT' (SDRT) with 24 Gy compared with an ultra HFX stereotactic body RT regime with 5x9 Gy, have been published [674].

Table 6.2.8: Selected trials on ultra-hypofractionation for intact localised PCa

Study	n	med FU (mo)	Risk-Group	Regimen (TD/fx)	Outcome
Widmark *et al.* 2019 HYPO-RT-PC [668]	1,200	60	89% intermediate 11% high	78 Gy / 39 fx, 8 wk. 42.7 Gy / 7 fx, 2.5 wk. No SBRT	FFS at 5 yr. 84% in both arms
Brand *et al.* 2019 PACE-B [671]	847	variable	8% low 92% intermediate	78 Gy / 39 fx, 8 wk. 36.25 Gy / 5 fx, 1-2 wk. SBRT	No difference in acute toxicity Grade ≥ 2 2-year GI 3% vs. 2%, p =ns Grade ≥ 2 2-year GU 2% vs. 3%, p =ns

FFS = failure-free survival; FU = follow-up; fx = number fractions; GI = gastro-intestinal toxicity; GU = genitourinary toxicity; mo. = months; n = number of patients; TD = total dose; SBRT = stereotactic body radiotherapy; wk. = weeks; yr. = years; ns=not significant.

6.2.3.1.4 Neoadjuvant or adjuvant hormone therapy plus radiotherapy

The combination of RT with luteinising hormone releasing hormone (LHRH) ADT has superiority compared with RT alone followed by deferred ADT on relapse, as shown by phase III RCTs [675-685] (Table 6.1.9). The main message is that for intermediate-risk disease a short duration of four to six months is optimal while a longer one, 2-3 years, is needed for high-risk patients. The largest RCT in intermediate risk disease comparing dose escalated RT with or without six months of ADT failed to demonstrate an OS advantage with a median follow-up time of 6.3 years. Six months of ADT use was associated with reduced PSA failure, fewer distant metastases and improved prostate cancer specific mortality [685].

Table 6.2.9: Selected studies of use and duration of ADT in combination with RT for PCa

Study	TNM stage	n	Trial	ADT	RT	Effect on OS
RTOG 85-31 2005 [676]	T3 or N1 M0	977	EBRT ± ADT	Orchiectomy or LHRH agonist 15% RP	65–70 Gy	**Significant benefit for combined treatment (p = 0.002) seems to be mostly caused by patients with ISUP grade group 2-5**
RTOG 94-13 2007 [680]	T1c–4 N0–1 M0	1,292	ADT timing comparison	2 mo. neoadjuvant plus concomitant vs. 4 mo. adjuvant suppression	Whole pelvic RT vs. prostate only; 70.2 Gy	**No significant difference between neoadjuvant plus concomitant vs. adjuvant androgen suppression therapy groups (interaction suspected)**
RTOG 86-10 2008 [677]	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.**
D'Amico AV, *et al.* 2008 [678]	T2 N0 M0 (localised unfavourable risk)	206	EBRT ± ADT	LHRH agonist plus flutamide for 6 mo.	70 Gy 3D-CRT	**Significant benefit that may pertain only to men with no or minimal co-morbidity** (HR: 0.55, 95% CI: 0.34-0.90, p = 0.01)
RTOG 92-02 2008 [681]	T2c–4 N0–1 M0	1554	Short vs. prolonged ADT	LHRH agonist given for 2 yr. as adjuvant after 4 mo. as neoadjuvant	65–70 Gy	p = 0.73, p = 0.36 **overall; significant benefit** (p = 0.044) (p = 0.0061) **in subset with ISUP grade 4–5**
EORTC 22961 2009 [682]	T1c–2ab N1 M0, T2c–4 N0–1 M0	970	Short vs. prolonged ADT	LHRH agonist for 6 mo. vs. 3 yr.	70 Gy 3D-CRT	**Better result with 3 yr. treatment than with 6 mo.** (3.8% improvement in survival at 5 yr.)
EORTC 22863 2010 [675]	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 yr. for combined treatment** (HR: 0.60, 95% CI: 0.45–0.80, p = 0.0004).

TROG 96-01 2011 [679]	T2b–4 N0 M0	802	Neoadjuvant ADT Duration	Goserelin plus flutamide 3 or 6 mo. before, plus concomitant suppression	66 Gy 3D-CRT	**No significant difference in OS reported; benefit in PCa-specific survival** (HR: 0.56, 95% CI: 0.32–0.98, p = 0.04) (10 yr.: HR: 0.84, 0.65–1.08, p = 0.18)
RTOG 99-10 2015 [683]	intermediate risk 94% T1–T2, 6% T3–4	1,579	Short vs. prolonged ADT	LHRH agonist 8 + 8 vs. 8 + 28 wk.	70.2 Gy 2D/3D	**67 vs. 68%,** p = 0.62, confirms 8 + 8 wk. LHRH as a standard
PCSIII 2020 [684]	Intermediate risk	600	76 Gy alone vs. 76 Gy + ADT vs. 70 Gy + ADT	LHRH + bicalutamide 6 mo. 4 mo. prior to RT	70 vs. 76 Gy	**Significantly improved biochemical failure-free and PCa-specific survival for ADT arms, with no difference in OS.**
RTOG 0815 2023 [685]	Intermediate risk	1,492	Dose escalated RT ± ADT	LHRH agonist/ antagonist + bicalutamide or flutamide 6 mo. 2 mo.prior to RT	79.2Gy (89%) 45Gy + BT boost (11%)	**No difference in OS. Significantly improved biochemical failure-free, metastatic-free survival and PCa-specific survival for ADT arm.**

ADT = androgen deprivation therapy; CI = confidence interval; EBRT = external beam radiotherapy in standard fractionation; HR = hazard ratio; ISUP = International Society of Urological Patholohy; LHRH = luteinising hormone-releasing hormone; mo. = months; n = number of patients; OS = overall survival; RP = radical prostatectomy; RT = radiotherapy; BT = brachytherapy; wk = week; yr. = year; 3D-CRT = three-dimensional conformal radiotherapy.

The question of the added value of EBRT combined with ADT has been clarified by 3 RCTs. All showed a clear benefit of adding EBRT to long-term ADT (Table 6.1.10).

Table 6.2.10: Selected studies of ADT in combination with, or without, RT for PCa

Study	TNM stage	n	Trial design	ADT	RT	Effect on OS
SPCG-7/ SFUO-3 2016 [686]	T1b-2 WHO Grade 1-3, T3 N0 M0	875	ADT ± EBRT	LHRH agonist for 3 mo. Plus continuous flutamide	70 Gy 3D-CRT vs. no RT	34% (95% CI: 29-39%) vs. 17% (95% CI: 13-22% CSM at 12 (15) yr. favouring combined treatment (p < 0.0001 for 15-yr. results) NCIC CTG PR.3/MRC
PRO7/NCIC 2015 [687]	T3-4 (88%), PSA > 20 ng/ mL (64%), ISUP grade group 4-5 (36%) N0 M0	1,205	ADT ± EBRT	Continuous LHRH agonist	65–70 Gy 3D-CRT vs. no RT	10-yr. OS = 49% vs. 55% favouring combined treatment HR: 0.7, p < 0.001)
Sargos, *et al.*, 2020 [688]	T3-4 N0 M0	273	ADT ± EBRT	LHRH agonist for 3 yr.	70 Gy 3D-CRT vs. no RT	Significant reduction of clinical progression; 5-yr. OS 71.4% vs. 71.5%

ADT = androgen-deprivation therapy; CSM = cancer-specific mortality; EBRT = external beam radiotherapy; HR = hazard ratio; LHRH = luteinising hormone-releasing hormone; mo. = months; n = number of patients; OS = overall survival; PSA = prostate-specific antigen; RT = radiotherapy; 3D-CRT = three-dimensional conformal radiotherapy; yr = years.

6.2.3.1.5 Combined dose-escalated radiotherapy and androgen-deprivation therapy

The combination of ADT with various forms of RT has been extensively studied, with extremely strong evidence for the use of such combined modality therapy in several settings. The MARCAP (Individual Patient Data Meta-Analysis of Randomised Trials in Cancer of the Prostate) consortium recently conducted a meta-analysis of trials using individual patient data (IPD), and a primary endpoint of MFS, a validated surrogate for OS. Trials were eligible if they studied the use or prolongation of ADT in patients receiving definitive RT, and included 12

trials with 10,853 patients. Median follow-up was over 11 years. The use of ADT was clearly associated with significant improvements in BCR, metastatic recurrence, MFS, and OS. The benefits of ADT were independent of RT dose, age, and risk groups comparing NCCN unfavourable intermediate-risk (see Sections 4.2 and 6.2.2.3), high-risk and locally-advanced disease. There were no demonstrable benefits from the extension of duration of neoadjuvant ADT [689].

Three RCTs have shown that the benefits of ADT are independent of dose escalation, and that the use of ADT would not compensate for a lower RT dose:

1. The GICOR study shows a better biochemical DFS in high-risk patients for 3D-CRT radiation dose > 72 Gy when combined with long-term ADT [690].
2. DART01/05 GICOR shows improved OS in high-risk patients after ten years if two years of adjuvant ADT is combined with high-dose RT [691].
3. The European Organisation for Research and Treatment of Cancer (EORTC) trial 22991 shows that six months ADT improves biochemical and clinical DFS irrespective of the dose (70, 74, 78 Gy) in intermediate-risk and low-volume high-risk localised PCa patients [692].

A meta-analysis based on IPD from two RCTs (RTOG 9413 and Ottawa 0101) has compared neoadjuvant/concomitant vs. adjuvant ADT (without substratifying between favourable- and unfavourable intermediaterisk disease) in conjunction with prostate RT and reported superior PFS with adjuvant ADT, but the data heterogeneity means that this observation is hypothesis-generating only [693].

In addition, a Canadian two-arm dose-escalated (76 Gy) RCT compared neoadjuvant and concomitant with adjuvant short-term ADT in 432 patients with intermediate-risk PCa. After ten years no significant difference in OS or RT-related grade ≥ 3 GI or GU toxicity was seen [694]. Therefore both regimen in combination with dose escalation are reasonable standards.

6.2.3.2 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.

One RCT on dose escalation (70.2 vs. 79.2 Gy) has incorporated protons for the boost doses of either 19.8 or 28.8 Gy. This trial shows improved outcome with the higher dose but it cannot be used as evidence for the superiority of proton therapy [645]. Thus, unequivocal information showing an advantage of protons over IMRT photon therapy is still not available. Studies from the SEER database and from Harvard describing toxicity and patient-reported outcomes do not point to an inherent superiority of protons [695, 696]. In terms of longer-term GI toxicity, proton therapy might even be inferior to IMRT [696].

A RCT comparing equivalent doses of proton-beam therapy with IMRT is underway. Meanwhile, proton therapy must be regarded as an experimental alternative to photon-beam therapy.

6.2.3.3 Spacer during external beam radiation therapy

Biodegradable spacer insertion involves using a liquid gel or balloon to increase the distance between the prostate and rectum and consequently reduce the amount of radiation reaching the rectum. Various materials have been used with most evidence available for CE-marked hydrogel spacers [697]. A meta-analysis including one RCT and six cohort studies using the hydrogel spacer demonstrated a 5–8% reduction in the rectal volume receiving high-dose radiation, although heterogeneity between studies is found [698]. In the final analysis of the RCT with a median follow-up of 37 months and with approximately two-thirds of patients evaluable, those treated with spacer *in situ* had no deterioration from baseline bowel function whilst those treated without spacer had a lower mean bowel summary score of 5.8 points which met the threshold for a minimally important difference of 4–6 points [699].

This meta-analysis highlights inconsistent reporting of procedural complications. In addition, with more widespread clinical use safety reports describe uncommon, but severe and life changing, complications including prostatic abscess, fistulae and sepsis [700]. Implantation is associated with a learning curve and should only be undertaken by teams with experience of TRUS and transperineal procedures with robust audit reporting in place [701]. Its role in the context of moderate or extreme HFX is as yet unclear.

6.2.3.4 Brachytherapy

6.2.3.4.1 Low-dose rate brachytherapy

Low-dose rate (LDR) BT uses radioactive seeds permanently implanted into the prostate. In patients declining or unsuitable for AS LDR monotherapy [702] can be offered to those with low-risk or NCCN favourable intermediate-risk and good urinary function defined as an International Prostatic Symptom Score (IPSS) < 12 and maximum flow rate > 15 mL/min on urinary flow tests [703]. The RTOG Ph3 RCT compared LDR BT +/- EBRT in participants with Gleason grade 6 and PSA < 20 or Gleason grade 7 and PSA < 10 and found that the addition of EBRT resulted in increased toxicity but no improvement in freedom from progression [704].

Patients having had a previous TURP can undergo BT without an increase in risk of urinary toxicity with due attention to dose distribution. A minimal channel TURP is recommended, leaving at least 1 cm rim of prostate tissue around the post-TURP urethral defect at the postero-lateral sides of the prostate and there should be at least a 3-month interval between TURP and BT to allow for adequate healing [705-708].

The only available RCT comparing RP and LDR BT as monotherapy was closed due to poor accrual [709]. Outcome data are available from a number of large population cohorts with mature follow-up [710-714]. The biochemical DFS for ISUP grade group 1 patients after five and ten years has been reported to range from 71% to 93% and 65% to 85%, respectively [710-714]. A significant correlation has been shown between the implanted dose and biochemical control [715]. A D90 (dose covering 90% of the prostate volume) of > 140 Gy leads to a significantly higher biochemical control rate (PSA < 1.0 ng/mL) after four years (92 vs. 68%). There is no OS benefit in adding neoadjuvant or adjuvant ADT to LDR monotherapy [716].

Low-dose rate BT can be combined with EBRT in NCCN unfavourable intermediate-risk PCa and high-risk patients. External beam RT (total dose of 78 Gy) has been compared with EBRT (total dose 46 Gy) followed by LDR BT boost (prescribed dose 115 Gy) in intermediate-risk and high-risk patients in the ASCENDE-RT randomised trial with twelve months of ADT in both arms [717, 718]. The LDR boost resulted in 5-, 7-year and 10-year PSA PFS increase (89%,86% and 85% respectively, compared to 84%,75%, 70%) but with no impact on distant metastasis or OS. This improvement in biochemical control was achieved at a cost of increased late grade 3+ GU toxicity (18% compared to 8%) and 2 treatment related deaths [718, 719]. Urinary toxicity was mainly in the development of urethral strictures and incontinence and great care should be taken during treatment planning.

6.2.3.4.2 High-dose rate brachytherapy

High-dose rate (HDR) BT uses a radioactive source temporarily introduced into the prostate to deliver radiation. The technical differences are outlined in Table 6.1.11. The use of the GEC (Groupe Europeen de Curietherapie)/ ESTRO Guidelines is strongly recommended [720]. High-dose rate BT can be delivered in single or multiple fractions and is often combined with EBRT of at least 45 Gy, conventionally fractionated [721]. A retrospective analysis on 1641 intermediate and high-risk patients demonstrated a better distant-metastasis free survival when a HDR BT boost was added to 50 – 54 Gy EBRT. The difference mounted to 12% at ten years [722]. A SR of non-RCTs and data from population studies suggest outcomes with EBRT plus HDR BT are superior to EBRT alone [723, 724].

A single-centre RCT of EBRT (55 Gy in 20 fractions) vs. EBRT (35.75 Gy in 13 fractions), followed by HDR BT (17 Gy in two fractions over 24 hours) has been reported [725]. In 218 patients with T1–3 N0M0 PCa the combination of EBRT and HDR BT showed a significant improvement in the biochemical disease-free rate (p = 0.04) at five and ten years (75% and 46% compared to 61% and 39%). However, an unexpectedly high 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 [725].

Supporting, but not definitive, evidence of the benefit of HDR boost is available from the TROG 03.04 RADAR trial. This multi-centre study had upfront radiation dose escalation (non-randomised) with dosing options of 66, 70, or 74 Gy EBRT, or 46 Gy EBRT plus HDR BT boost and randomised men with locally-advanced PCa to 6 or 18 months ADT. After a minimum follow-up of ten years HDR boost significantly reduced distant progression, the study primary endpoint (sub HR: 0.68, 95% CI: 0.57–0.80; p < 0.0001), when compared to EBRT alone and, independent of duration of ADT, HDR boost was associated with increased IPSS of 3 points at 18 months post-treatment resolving by three years but decreased rectal symptoms when compared to EBRT [726]. Although radiation dose escalation using BT boost provides much higher biological doses, the TROG 03.04 RADAR RCT and SRs show ADT use independently predicts better outcomes regardless of radiation dose intensification [716, 726, 727]. Omitting ADT may result in inferior OS and based on current evidence ADT use and duration should be in line with that used when delivering EBRT alone.

Fractionated HDR BT as monotherapy can be offered to patients with low- and intermediate-risk PCa, who should be informed that results are only available from limited series in very experienced centres. Five-year PSA control rates of 97.5% and 93.5% for low- and intermediate-risk PCa, respectively, are reported, with late grade 3+ GU toxicity rates < 5% and no, or very minimal, grade 3+ GI toxicity rates [728]. Single fraction HDR monotherapy should not be used as it has inferior biochemical control rates compared to fractionated HDR monotherapy [729].

Table 6.2.11: Difference between LDR and HDR brachytherapy

	Differences in prostate brachytherapy techniques
Low dose rate (LDR)	• Permanent seeds implanted • Uses Iodine-125 (I-125) (most common), Palladium-103 (^{103}Pd-) or Cesium-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 • Iridium-192 (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

6.2.3.5 Acute side effects of external beam radiotherapy and brachytherapy

Gastro-intestinal and urinary side effects are common during and after EBRT. In the EORTC 22991 trial, approximately 50% of patients reported acute GU toxicity of grade 1, 20% of grade 2, and 2% grade 3. In the same trial, approximately 30% of patients reported acute grade 1 GI toxicity, 10% grade 2, and less than 1% grade 3. Common toxicities included dysuria, urinary frequency, urinary retention, haematuria, diarrhoea, rectal bleeding and proctitis [730]. In addition, general side effects such as fatigue are common. It should be noted that the incidence of acute side effects is greater than that of late effects (see Section 8.2.2.1), implying that most acute effects resolve. In a RCT of conventional dose EBRT vs. EBRT and LDR BT the incidence of acute proctitis was reduced in the BT arm, but other acute toxicities were equivalent [717]. Acute toxicity of HDR BT has not been documented in a RCT, but retrospective reports confirm lower rates of GI toxicity compared with EBRT alone and grade 3 GU toxicity in 10%, or fewer, patients, but a higher incidence of urinary retention [731]. Similar findings are reported using HFX; in a pooled analysis of 864 patients treated using extreme HFX and stereotactic RT, declines in urinary and bowel domains were noted at three months which returned to baseline, or better, by six months [732].

6.2.4 ***Investigational therapies***

6.2.4.1 Background

Besides RP, EBRT and BT, other modalities have emerged as potential therapeutic options in patients with clinically localised PCa [733-735]. These new modalities have been developed as minimally invasive procedures with the aim of providing equivalent oncological safety, reduced toxicity, and improved functional outcomes. In this section, both whole gland- and focal treatment [736, 737] will be considered, looking particularly at high-intensity focused US (HIFU), cryotherapeutic ablation of the prostate (cryotherapy) and focal photodynamic therapy (PDT), as sufficient data are available to form the basis of some initial judgements. Other options such as radiofrequency ablation (RFA) and electroporation, among others, are considered to be in the early phases of evaluation [736].

6.2.4.2 Whole-gland therapies

6.2.4.2.1 Cryotherapy for whole-gland treatment

Cryotherapy uses freezing techniques to induce cell death by dehydration resulting in protein denaturation, direct rupture of cellular membranes by ice crystals and vascular stasis and microthrombi, resulting in stagnation of the microcirculation with consecutive ischaemic apoptosis [733-735]. Freezing of the prostate is ensured by the placement of 17-gauge cryo-needles under TRUS guidance, placement of thermosensors at the level of the external sphincter and rectal wall, 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 cryotherapy devices are mainly used. Since its inception, cryotherapy has been used for whole-gland treatment in PCa either as a primary or salvage treatment option.

The main adverse effects of whole-gland cryosurgery are ED (18%), urinary incontinence (2–20%), urethral sloughing (0–38%), rectal pain and bleeding (3%) and recto-urethral fistula formation (0–6%) [738]. There is a lack of prospective comparative data regarding oncological outcomes of whole-gland cryosurgery as a curative treatment option for men with localised PCa, with most studies being non-comparative single-arm case series with short follow-up [738].

6.2.4.2.2 High-intensity focused ultrasound for whole-gland treatment

High-intensity focused US consists of focused US waves emitted from a transducer that cause tissue damage by mechanical and thermal effects as well as by cavitation [739]. The goal of HIFU is to heat malignant tissue above 65°C, so that it is destroyed by coagulative necrosis. High-intensity focused US is performed under general or spinal anaesthesia, with the patient lying in the lateral or supine position. Since the ultrasound energy is most often delivered from the rectal cavity, HIFU faces challenges in delivering energy to the anterior part in large prostates.

High-intensity focused US has previously been widely used for whole-gland therapy with the following adverse effects: acute urinary retention (10%), ED (23%), urethral stricture (8%), rectal pain or bleeding (11%), recto-urethral fistula (0–5%) and urinary incontinence (10%) [738]. Combining the whole-gland HIFU treatment with TUR-P reduces the rate of urethral strictures, maintains the level of incontinence, but increases the rate of ED [740].

Overall, the lack of any long-term prospective comparative studies, and data to suggest poor long-term oncological outcomes for men with high-risk localised disease [741] prevents whole-gland HIFU from being considered as a reasonable alternative to the established curative treatment options [738]. In addition, the expected improvements in functional outcome failed to materialise with 12% of patient developing incontinence and 61% developing ED [742].

6.2.4.3 Focal therapy

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 that men are identified at an earlier stage with smaller tumours, with a greater propensity for unifocal disease potentially suitable for focal therapy [743-745]. There is also greater awareness of the risks of the consequences of treatment leading to attempts to ablate only a region of the prostate containing the tumour thereby limiting toxicity by sparing the neurovascular bundles, sphincter, and urethra [746-748]. The question remains which if any of these small unifocal tumours need treatment.

A SR included data from 5,827 patients across 72 studies and covered different energy sources including HIFU, cryotherapy, PDT, laser interstitial thermotherapy, focal BT, irreversible electroporation (IRE) and radiofrequency ablation (RFA) [749]. The review favours HIFU and PDT for their higher quality data, over 95% of pad-free incontinence and 85–90% of patients without clinically significant cancer in short-term analysis. This has to be critically analysed, because 45% of all patients with a focal approach included in this SR had an ISUP Grade Group 1 cancer. The overall quality of the evidence was low, due to the majority of studies being single-centre, non-comparative and retrospective in design, heterogeneity of definitions and approaches, follow-up strategies, outcomes, and duration of follow-up. Although the review finds high quality evidence that focal therapy has favourable functional outcomes and minimises AEs, definitive proof of oncological effectiveness of focal therapy compared to standard treatments remains unavailable.

The currently largest analysis on oncologic outcomes following focal HIFU includes 625 patients, with 70% having ISUP grade group 2/3 disease, followed for five years with an 88% failure-free survival (FFS), defined as the need for salvage treatment or systemic therapy [750]. In this study one repeated focal HIFU session was allowed and performed in 25% of all patients. Follow-up was driven by PSA and clinics, with re-biopsies performed only in 36% of patients after a significant PSA rise and suspicious MRI.

The guideline panel acknowledges the challenges for interventional RCTs [751-753]. The interim analysis and meeting reports demonstrate slow recruitment, patients declining consent and rejecting their treatment allocation into the RP group. In an attempt to overcome this propensity-matched analysis using prospective multi-centre databases have been performed for comparison of focal therapy vs. radical therapy [754, 755]. Such analyses are always susceptible to unmeasured selection biases in who was selected for each treatment.

Oncological follow-up data up to 8 years can be used to counsel patients in treatment decisions [754]. Patients were managed by focal therapy had a HIFU or cryotherapy, with one retreatment, if needed. 17.1% of patients

in the focal arm received a retreatment. The primary outcome was FFS defined as "need for local or systemic salvage treatment or metastasis". Both groups included 246 patients with an average PSA of 7.9 ng/mL and 60% ISUP Grade Group 2/3 cancers. The cancer core length was 5–6 mm with 45% having bilateral cancer. The authors report similar cancer control 8 years after therapy, with FFS and BCR of 83% and 23.9% for focal therapy vs. 79% and 24.8% for RP, respectively. Similar results were demonstrated in a cohort-based analysis with a follow-up six years [755]. The use of different definitions for oncological failure in the two arms is another limitation of these studies. While any recurrence after RP was seen as failure, a second HIFU was permitted in the focal group. The current data from the HIFU Evaluation and Assessment of Treatment (HEAT) registry indicates that a repeat-HIFU does not significantly decrease urinary or erectile function [756]. However, this change of failure definition will have to be re-evaluated. It is important to note, that these results were achieved in centres with a dedicated focal program where all patients had a mpMRI with targeted and systematic biopsies or full template mapping biopsies.

The prospective HEAT registry analysed over 800 men undergoing focal HIFU for localised PCa [756]. The functional data indicate low treatment-related toxicity with less than 4% decrease in pad-free incontinence and a reduction in IIEF of 0.4 points. The impact of salvage therapies after focal therapy was investigated in small series [757, 758]. If a salvage RP is necessary, the reported functional and oncological outcomes are comparable to treatment-naive patients [802, 803].

One comparative RCT was conducted in a very-low risk population, for which there is currently a strong movement away from any form of active treatment. This study was comparing padeliporfin-based vascular targeted PDT vs. AS and found at a median follow-up of 24 months that less patients progressed in the PDT arm compared with the AS arm (adjusted HR: 0.34, 95% CI: 0.24–0.46), and needed less radical therapy (6% vs. 29%, $p < 0.0001$). Updated results were published in 2018 showing that these benefits were maintained after four years [759]. Nevertheless, limitations of the study include an unusually high observed rate of disease progression in the AS arm (58% in two years) and more patients in the AS arm chose to undergo radical therapy without a clinical indication which may have introduced confounding bias. Finally, the AS arm did not undergo any confirmatory biopsy or any MRI scanning, which is not representative of contemporary practice. A matched-pair analysis comparing focal cryo therapy to AS with 76% ISUP grade group 1 cancers failed to demonstrate any significant advantages for MFS and OS [760].

The available evidence indicates that focal therapy is associated with less AEs than whole gland or radical treatments. Many of the patients included in these trials would currently be considered to have been over treated. Robust prospective trials reporting standardised 15-year oncological outcomes [761] are needed in patients with clinically significant cancers before unrestricted recommendations in support of focal therapy for routine clinical practice can be made [736, 750, 761]. Currently, focal therapy using HIFU or cryotherapy should be performed within the context of a prospective registry. All other ablative modalities and treatment strategies should only be offered in well-designed prospective trial setting. In order to allow quality analysis of the collected data, the prospective registry should adhere to the EMA recommendations (Guideline on registry-based studies EMA/426390/2021), which emphasises the need for clear follow-up timelines and timely recording, completeness of core data of consecutive patients enrolled, an analysis plan in defined intervals and a data quality management. In near future the EAU will offer a quality registry within the PIONEER network.

*6.2.5 General guidelines for the treatment of prostate cancer**

Recommendations	Strength rating
Offer a watchful waiting (WW) policy to asymptomatic patients with clinically localised disease and with a life expectancy < ten years (based on comorbidities and age).	Strong
No active treatment modality has shown superiority over any other active management options or deferred active treatment in terms of overall- and PCa-specific survival for clinically localised low/intermediate-risk disease.	Strong
Inform patients that all local treatments have side effects.	Strong
Surgical treatment	
Inform patients that no surgical approach (open-, laparoscopic- or robotic RP) has clearly shown superiority in terms of functional or oncological results.	Weak
Consider avoiding nerve-sparing surgery when there is a risk of ipsilateral ex-tra-capsular extension (based on cT stage, ISUP grade group, magnetic reso-nance imaging, or with this information combined in a nomogram).	Weak

In patients undergoing a lymph node dissection you should perform an extended PLND.	Strong
Do not offer neoadjuvant androgen deprivation therapy before surgery.	Strong
Radiotherapeutic treatment	
Offer intensity-modulated radiation therapy (IMRT) or volumetric arc radiation therapy (VMAT) plus image-guided radiation therapy (IGRT) for definitive treatment of PCa by external-beam radiation therapy.	Strong
Offer moderate hypofractionation (HFX) with IMRT/VMAT plus IGRT to the prostate to patients with localised disease (60 Gy/20 fractions in 4 weeks or 70 Gy/28 fractions in 6 weeks).	Strong
Offer low-dose rate (LDR) brachytherapy monotherapy to patients with good urinary function and low-risk or NCCN favourable intermediate-risk disease.	Strong
Offer LDR or high-dose rate (HDR) brachytherapy boost combined with IMRT/VMAT plus IGRT to patients with good urinary function and NCCN unfa-vourable intermediate-risk or high-risk disease and/or locally-advanced disease.	Weak
Active therapeutic options outside surgery or radiotherapy	
Offer focal therapy with HIFU or cryotherapy within a clinical trial or prospective registry.	Strong

**All recommendations are based on conventional imaging with isotope bone scan and CT/MR abdomen/pelvis.*

Summary of evidence	**LE**
The AS strategy should be based on PSA (at least once every six months), serial DRE (at least once yearly) and repeated biopsy. Serial DRE may be omitted if MRI is stable.	3
Serial MRI can improve the detection of aggressive cancers during AS.	
A progression on MRI mandates a repeat biopsy before a change in treatment strategy.	
A stationary MRI does not make repeat biopsy superfluous (patients with low-risk tumour and a stable PSA-D < 0.15 may be excepted).	

Recommendations	**Strength rating**
Base the strategy of active surveillance (AS) on a strict protocol including digital rectal examination (at least once yearly), prostate-specific antigen (PSA) (at least once every six months) and repeated biopsy every 2 to 3 years.	Strong
Patients with a low risk PCa, a stable MRI (PRECISE 3) and a stable, low PSA density (< 0.15) may be excused from repeat biopsy.	Weak
Perform magnetic resonance imaging (MRI) and repeat biopsy if PSA is rising (PSA-doubling time < 3 years).	Strong
Base change in treatment on biopsy progression, not on progression on MRI and/or PSA.	Weak
Re-classify patients with low-volume ISUP grade group 2 disease included in AS protocols, if repeat non-MRI-based systematic biopsies performed during monitoring reveal > 3 positive cores or maximum core involvement > 50%/core of ISUP grade group 2 disease.	Weak

6.3 Treatment by disease stages

6.3.1 Treatment of low-risk disease

6.3.1.1 Active surveillance

The main risk for men with low-risk disease is over-treatment (see sections 6.1.1, 6.2.1); AS should therefore be considered SOC for all such patients with a life expectancy > ten years based on comorbidities and age) and where curative treatment would be considered in the case of disease progression.

6.3.1.1.1 Active surveillance - inclusion criteria

Guidance regarding selection criteria for AS is limited by the lack of data from prospective RCTs. As a consequence, the Panel undertook an international collaborative study involving healthcare practitioners and patients to develop consensus statements for deferred treatment with curative intent for localised PCa, covering all domains of AS (DETECTIVE Study) [330], as well as a formal SR on the various AS protocols [491]. The criteria most often published include: ISUP grade group 1, clinical stage cT1c or cT2a, PSA < 10 ng/mL and PSA-D < 0.15 ng/mL/cc, as based on systematic biopsy schemes [487, 492]. The latter threshold remains controversial [492, 493]. These criteria were supported by the DETECTIVE study consensus. There was no agreement on

the maximum number of systematic cores that can be involved with cancer or the maximum percentage core involvement (CI), although there was recognition that extensive disease on MRI should exclude men from AS, even though there is no firm definition on this, especially when targeted biopsies confirm ISUP grade group 1 [330]. A SR and meta-analysis found three clinico-pathological variables which were significantly associated with reclassification, high PSA-D, > 2 positive cores (on systematic biopsies) and African-American descent [495]. In addition, a previous pathology consensus group suggested excluding men from AS when any of the following features were present: predominant ductal carcinoma (including pure IDC), cribriform histology, sarcomatoid carcinoma, small cell carcinoma, EPE or LVI in needle biopsy [497] and perineural invasion [498].

A multi-disciplinary consensus conference on germline testing attempted to develop a genetic implementation framework for the management of PCa [154]. Based on consensus, *BRCA2*-gene testing was recommended for AS discussions and could be performed in men with family history of prostate, breast or ovarian cancers. However, the nature of such discussions and how a positive result influences management were beyond the scope of the project. Currently, *BRCA2* mutation does not exclude a patient from AS if tumour factors are otherwise favourable. Furthermore, if included in AS programmes, patients with a known *BRCA2* mutation should be cautiously monitored until such time that more robust data are available.

6.3.1.1.2 Tissue-based prognostic biomarker testing for selection for active surveillance

Biomarkers, including Oncotype Dx®, Prolaris®, Decipher®, PORTOS and ProMark® are promising (see Section 5.2.8.3). However, further data will be needed before such markers can be used in standard clinical practice [220].

6.3.1.1.3 Magnetic resonance imaging for selection for active surveillance

In men eligible for AS based upon systematic biopsy findings alone who did not have a pre-biopsy MRI, a re-biopsy within 6–12 months (usually referred to as 'confirmatory biopsy') seems mandatory to exclude sampling error. A large body of literature including two RCTs showed that adding MRI-targeted biopsy to systematic sampling at confirmatory biopsy improved detection of ISUP grade ≥ 2 cancers and thus, patient selection for AS [121, 499, 500, 502-504]. Adding MRI-targeted biopsy to systematic sampling at confirmatory biopsy improved upgrade detection by increments of 0-7.9 per 100 men depending on the series [499]. In a meta-analysis of 6 studies, the rate of upgrading to ISUP grade group ≥ 2 cancer increased from 20% (95% CI: 16–25%) to 27% (95% CI: 22–34%) when MRI-targeted biopsy was added to systematic biopsy [504]. The Active Surveillance MRI Study (ASIST) randomised men on AS scheduled for confirmatory biopsy to either 12-core systematic biopsy or to MRI with targeted biopsy (when indicated), combined with systematic biopsy (up to 12 cores in total). After two yearsof follow-up, use of MRI before confirmatory biopsy resulted in fewer failures of surveillance (19% vs. 35%, p = 0.017) and in fewer patients progressing to ISUP grade group ≥ 2 cancer (9.9% vs. 23%, p = 0.048) [502]. However, systematic biopsy retains its additional value, which argues for a combined biopsy approach [499, 504]. The DETECTIVE study agreed that men eligible for AS after combined systematic- and MRI-targeted biopsy do not require a confirmatory biopsy [330].

If the PCa diagnosis is made on MRI-targeted biopsy alone (recommended in some countries national guidelines, e.g., the Nordic countries [762] in order to lower the risk of over-detection of insignificant tumours, a confirmative systematic biopsy should be performed before definite decision of AS to rule out more widespread cancer growth in the prostate.

6.3.1.1.4 Follow-up during active surveillance

Based on the DETECTIVE consensus study, the follow-up strategy should be based on serial DRE (at least once yearly), PSA (at least once, every six months) and repeated biopsy. It was also agreed that PSA progression or change in PSA kinetics alone should lead to reclassification only if accompanied by changes in histology on repeat biopsy [330].

Yerram *et al.*, analysed a prospectively-maintained AS cohort of 369 patients (272 with ISUP grade group 1 cancer and 97 with ISUP grade group 2 cancer) who had been selected for AS after combined systematic and MRI-targeted sampling during confirmatory biopy. At two years, systematic biopsy, MRI-targeted biopsy and combined biopsy detected grade progression in 44 patients (15.9%), 73 patients (26.4%) and 90 patients (32.5%), respectively. This suggests that both biopsy approaches retain added value, not only for confirmatory biopsy, but also during AS [763].

In 2016, the Prostate Cancer Radiological Estimation of Change in Sequential Evaluation (PRECISE) criteria were established to standardise the assessment of tumour progression on serial MRI [507]. Progression on MRI, defined using the PRECISE criteria, or not, is a strong predictor of histological upgrading [508, 509]. Two independent meta-analyses assessed the value of MRI progression criteria for predicting histological progression (mostly defined as progression to ISUP grade group ≥ 2). The pooled histological progression rate was 27% in both reviews. If biopsies were triggered only by MRI progression findings, approximately two thirds of the biopsies would be avoided, at the cost of missing 40% of men with histological progression. In addition, at least half of biopsied men would have had negative findings for histological progression and thus would have undergone unnecessary biopsies. If histological progression was restricted to progression to ISUP grade group > 3, approximately 30% of histological progression would be missed and approximately 80% of the biopsies performed would be unnecessary. The use of the PRECISE criteria did not seem to change these results [510, 511]. This supports maintaining protocol-mandated follow-up biopsies during the course of AS.

However, several factors have been found to be associated with low re-classification rates and long PFS; negative baseline or follow-up MRI [505, 512-518], low PSA-D [505, 513, 515, 518], low PSA velocity [519, 520] or negative biopsy (i.e., no cancer at all) at confirmatory or follow-up biopsy [521]. In patients with stable (PRECISE 3) follow-up MRI, a low PSA-D may be associated with a low rate of progression [522]. Using these criteria, it might be possible, in the future, to create risk-based personalised AS biopsy schedules.

A Panel SR incorporating 263 surveillance protocols showed that 78.7% of protocols mandated per-protocol confirmatory biopsies within the first two yearsand that 57.7% of the protocols performed repeat biopsy at least every three years for ten years after the start of AS [491]. In another review it was concluded that a negative follow-up biopsy was associated with a 50% decrease in the risk of future reclassification and upgrading [523]. In a single-centre AS cohort of 514 patients who underwent at least three protocol-mandated biopsies after diagnosis (the confirmatory biopsy and at least two additional surveillance biopsies), men with one negative biopsy (i.e., no cancer at all) at confirmatory or second biopsy, or men with two consecutive negative biopsies had a lower likelihood of a positive third biopsy and significantly better 10-year treatmentfree survival [521]. This suggests that men with repetitive negative biopsies may pursue AS with at least less frequent untriggered biopsies.

6.3.1.1.5 Active Surveillance - change in treatment

Men may remain on AS whilst they continue to consent, have a life expectancy of > ten years and the disease remains indolent. Patient anxiety about continued surveillance occurs in around 10% of patients on AS [524] and was recognised as a valid reason for active treatment [330]. A thorough discussion on pros/cons of AS vs. active treatment already at the time of diagnosis is therefore of outmost importance. More common is the development of other comorbidities which may result in a decision to transfer to a WW strategy.

A PSA change alone (including PSA-DT < 3 years) should not change management based on its weak link with grade progression [527, 528] but rather trigger further investigation. There was clear agreement in the DETECTIVE consensus meeting that a change in PSA should lead to repeat-MRI and repeat-biopsy. It was also agreed that changes on follow-up MRI needed a confirmatory biopsy before considering active treatment [330].

However, the histopathology criteria required to trigger a change in management in the targeted biopsy era remain debated. Magnetic resonance imaging-targeted biopsy induces a grade shift and ISUP grade group 2–3 cancers detected by MRI-targeted biopsy have, on average, a better prognosis than those detected by systematic sampling (see Section 5.2.4.2.6.4). As an increasing number of men with favourable intermediate-risk disease are managed with AS (see section 6.2.2.1), it seems illogical to use progression to ISUP grade group 2 based on targeted biopsies as the sole criterion for reclassification. In addition, as acknowledged in the DETECTIVE consensus meeting, the number of positive cores is not an indicator of tumour volume anymore if targeted biopsies are performed [330, 529]. No agreement could be reached on the pathological criteria required to trigger a change in management during the DETECTIVE consensus meeting [330]. However, based on the findings of a SR incorporating 271 reclassification protocols, patients with low-volume ISUP grade group 2 disease at recruitment, and with increased systematic core positivity (> 3 cores involvement [> 50% per core]) on repeat systematic biopsies not using MRI, should be reclassified [491].

6.3.1.2 Alternatives to active surveillance

For patients with a life expectancy of < ten years (based on comorbidities and age), where curative treatment would not be an option in the case of progression, WW is SOC rather than AS.

In terms of alternatives to AS in the management of patients with low-risk disease there is some data from randomised studies. In the PIVOT trial (Section 6.1.1) which compared surgery vs. observation, only 42%

of patients had low-risk disease [482]. Sub-group analysis revealed that for low-risk disease there was no statistically significant difference in all-cause mortality between surgery vs. observation (RR: 0.93, 95% CI: 0.78–1.11). In the ProtecT study (Section 6.1.1) which compared the less organised strategy of "active monitoring" (i.e. repeat PSA management only) vs. surgery vs. EBRT, 66% of patients had a D'Amico low-risk disease [474]. The study found, after 15 years follow-up, no difference between the three arms in terms of OS and CSS, but AM had higher metastatic progression (9.4%) compared with surgery (4.7%) or EBRT (5.0%). There are no robust data comparing contemporary AS protocols with either surgery or EBRT in patients with low-risk disease. Active surveillance should be considered SOC in patients with low- to intermediate risk disease and a life expectancy > ten years. Surgery and EBRT should only be considered as alternatives to AS in patients suitable for such treatments after thorough information on pros and cons of AS and active treatment, and who after such information refuse or for some other reason are deemed unfit for AS, and who accept a trade-off between toxicity and prevention of disease progression.

Other treatments such as whole-gland ablative therapy (e.g. cryotherapy or HIFU) or focal ablative therapy remain unproven in the setting of localised low-risk disease compared with AS or radical treatment options and should not be used outside a trial setting or well-designed prospective cohort setting. These treatments are discussed in detail in Section 6.1.5.

6.3.1.2.1 Androgen deprivation monotherapy

Data regarding the use of ADT monotherapy in men with low-risk localised disease may be inferred indirectly from the Early Prostate Cancer (EPC) Trial Programme which published its findings in 2006 [764]. The EPC programme comprises three large RCTs including 8,113 men with localised (cT1–2, N0/NxM0) or locally advanced (cT3–4, any N; or any T, N+, M0) PCa. The intervention was oral bicalutamide 150 mg monotherapy vs. placebo following standard care (defined as RP, radical EBRT or WW). The primary endpoints were PFS and OS. Patients were stratified according to clinical stage only; data regarding PSA and GS were not assessed. The authors found in patients with localised disease, ADT monotherapy did not improve PFS nor OS in any of the subgroups, compared with placebo. Instead, there was a statistically insignificant numerical trend towards worse OS with ADT in the WW sub-group (HR: 1.16, 95% CI: 0.99–1.37; p = 0.07). Although the trial did not directly address men with low-risk disease, it offered some evidence suggesting that otherwise asymptomatic men with localised disease should not receive ADT monotherapy. A phase 2 RCT addressed a similar approach, where patients were randomised to enzalutamide plus AS or AS alone. This study indicated that PSA progression could be delayed, and the odds of a negative biopsy increased during the median follow-up time of 1.3 years, but patients had more side effects of the treatment without showing any long-term benefits of the treatment [765]. Hence, there is no evidence supporting the use of any hormonal treatment in asymptomatic men with low-risk disease who are not eligible for any local/radical treatment; these men should simply be offered AS or WW alone.

*6.3.1.3 Summary of evidence and guidelines for the management of low-risk disease**

Summary of evidence	**LE**
WW or AS is SOC, based on life expectancy.	2a
All active treatment options present a risk of over-treatment.	1a

Recommendations	**Strength rating**
Watchful Waiting	
Manage patients with a life expectancy < ten years by watchful waiting.	Strong
Active surveillance (AS)	
Manage patients with a life expectancy > ten years and low-risk disease by AS.	Strong
Selection of patients	
Patients with cribriform or intraductal histology on biopsy should be excluded from AS.	Strong
Perform magnetic resonance imaging (MRI) before a confirmatory biopsy if no MRI has been performed before the initial biopsy.	Strong
Take both targeted biopsy (of any PI-RADS ≥ 3 lesion) and systematic biopsy if a confirmatory biopsy is performed.	Strong
If MRI is not available, per-protocol confirmatory prostate biopsies should be performed.	Weak

If a patient has had upfront MRI followed by systematic and targeted biopsies there is no need for confirmatory biopsies.	Weak
Strategy of surveillance	
Repeat biopsies should be performed at least once every three years for ten years.	Weak
In case of prostate-specific antigen progression or change in digital-rectal exam-ination or MRI findings, do not progress to active treatment without a repeat biopsy.	Strong

6.3.2 Treatment of intermediate-risk disease

When managed with non-curative intent, intermediate-risk PCa is associated with 10-year and 15-year PCSM rates of 13.0% and 19.6%, respectively [841]. These estimates are based on systematic biopsies and may be overestimated in the era of MRI-targeted biopsies.

6.3.2.1 Active Surveillance

In the ProtecT trial, where 34% of the randomised patients had a D'Amico intermediate- or high-risk disease, there was no statistically significant difference in CSS at 15 years [474]. In the comprehensive characterisation of the patients in the ProtecT trial, treatment received, PSA, ISUP grade group at diagnosis, cT stage, risk group, number of PCa-involved biopsy cores, maximum length of tumour (median 5.0 vs. 3.0 mm), aggregate length of tumour (median 8.0 vs. 4.0 mm), and presence of perineural invasion were each associated with increased risk of disease progression ($p < 0.001$ for each). However, these factors could not reliably predict progression in individuals [487].

The outcomes of AS in intermediate-risk PCa has also been analysed in three SRs and meta-analyses, summarising available data on its oncological outcomes and comparing patients with intermediate-risk PCa to patients with low-risk disease [766-768]. The definition of AS was not strictly defined in either of the reviews: instead, the search strategies included 'active surveillance' as a search term, and no *a priori* study protocol was available. The primary outcome was the proportion of patients who remained on AS, whilst secondary outcomes included CSS, OS, and MFS in all three studies. In the first review 17 studies were included, incorporating 6,591 patients with intermediate risk disease. Sixteen studies included patients with low- and intermediate-risk disease, hence enabling comparative outcome assessment via pooled analysis. Only one study performed MRI at recruitment and during AS. There was significant clinical heterogeneity in terms of inclusion criteria for intermediate-risk disease. The results showed the proportion of patients who remained on AS was comparable between the low- and intermediate-risk groups after ten- and fifteen-years' follow-up (OR: 0.97, 95% CI: 0.83–1.14; and OR: 0.86, 95% CI: 0.65–1.13, respectively). Cancer-specific survival was worse in the intermediate-risk group after ten years (OR: 0.47, 95% CI: 0.31–0.69) and 15 years (OR: 0.34, 95% CI: 0.2–0.58). Overall survival was not statistically significantly different at five years' follow-up (OR: 0.84, 95% CI: 0.45–1.57) but was significantly worse in the intermediate-risk group after ten years (OR: 0.43, 95% CI: 0.35–0.53). Metastases-free survival did not significantly differ after five years (OR: 0.55, 95% CI: 0.2–1.53) but was worse in the intermediate-risk group after ten years (OR: 0.46, 95% CI: 0.28–0.77) [768]. The second review, including 25 studies and a total of 29,673 low- or intermediate-risk patients, showed similar results in terms of treatment-free survival at ten years (RR: 1.16, 95% CI: 0.99-1.36), risk of developing metastases (RR: 5.79, 95% CI: 4.61-7.29), risk of dying from PCa (RR: 3.93, 95% CI: 2.93-5.27) and risk of dying from any cause (RR: 1.44, 95% CI: 1.11-1.86) [766]. The third, most recent, review included 25 studies of which thirteen studies provided data on treatment free survival, six on CSS and seven on OS. Treatment free survival was not statistically significantly different in the intermediate risk group after 5 (RR: 0.92, 95% CI: 0.82-1.02), 10 (RR: 0.83, 95% CI: 0.55-1.23) or 15 years (RR: 0.54, 95% CI: 0.21-1.39). Cancer-specific survival was significantly lower after 15 years (RR: 0.92, 95% CI: 0.89-0.96) and OS was significantly lower after ten years (RR: 0.87, 95% CI: 0.82-0.93) in the intermediate risk group. It should be noted that many of the studies included patients with ISUP grade group 3 disease. When these studies were excluded no difference in treatment free, cancer specific or OS could be observed [767].

In a subgroup analysis of four studies comparing outcomes of patients with intermediate- and low-risk PCa of ISUP grade group ≤ 2 (n = 1,900) no statistically significant difference could be found in terms of treatment free survival or risk of developing metastases (RR: 1.03, 95% CI: 0.62-1.71 and RR: 2.09, 95% CI: 0.75-5.82, respectively). Both reviews indicate that AS in unselected intermediate-risk patients implies a higher risk of progression over time. It remains unclear whether this difference only reflects the inborne difference in outcome, that can also be seen when comparing immediate treatment of low- and intermediate-risk PCa, or if the delay in treatment caused any worsening of the outcomes in the intermediate-risk group in any way. All three reviews conclude that AS could be offered to patients with intermediate-risk disease, but they should be informed of a higher risk of progression and the latter two reviews suggests limiting the inclusion of intermediate-risk patients to those with low-volume ISUP grade group 2 disease.

A Canadian consensus group proposes that low volume ISUP grade group 2 (< 10% Gleason pattern 4 on systematic biopsies) may also be considered for AS. These recommendations have been endorsed by the ASCO [225] and the DETECTIVE study consensus [330] for those patients with a PSA < 10 ng/mL and low core positivity. The DETECTIVE Study concluded that men with favourable ISUP grade group 2 PCa (PSA < 10 ng/mL, low density, clinical stage ≤ cT2a and a low number of positive systematic cores) should also be considered for deferred treatment [330]. In this setting, re-biopsy within six to twelve months to exclude sampling error is even more relevant than in low-risk disease [492, 769]. The DETECTIVE Study-related qualitative SR aimed to determine appropriate criteria for inclusion of intermediate-risk disease into AS protocols [491]. Out of 371 AS protocols included in the review, more than 50% included patients with intermediate-risk disease on the basis of PSA up to 20 ng/mL (25.3%), ISUP grade group 2 or 3 (27.7%), clinical stage cT2b/c (41.6%) and/or direct use of D'Amico risk grouping of intermediate risk or above (51.1%). The DETECTIVE study reached consensus that patients with ISUP grade group 3, or patients with intraductal or cribriform histology, should not be considered for AS. The presence of any grade 4 pattern is associated with a 3-fold increased risk of metastases compared to ISUP grade group 1, while a PSA up to 20 ng/mL might be an acceptable threshold [769-771], especially in the context of low PSA-D. In addition, it is likely that MRI and targeted biopsies will detect small foci of Gleason grade 4 cancer that might have been missed with systematic biopsy. Therefore, care must be taken when explaining this treatment strategy, especially to patients with the longest life expectancy.

There is no clear consensus on how to interpret MRI and targeted biopsies for AS but the DETECTIVE study consensus was that if targeted biopsies based upon mpMRI images are performed, the number of positive cores of the targeted biopsies are not an indicator of the extent of disease or tumour volume. Indicator of the tumour volume may be either the number of positive cores, and the length of cancer in each core, based on systematic biopsies, or the volume of the dominant lesion seen on mpMRI [330].

In summary, AS can be considered in patients with a life expectancy of more than ten years and low-volume ISUP grade group 2 (defined as ≤ 3 positive systematic cores and ≤ 50% core involvement) or another single element of intermediate-risk disease (i.e. favourable intermediate-risk disease). Patients with ISUP grade group 3 disease, or patients with intraductal or cribriform histology, should be excluded. The monitoring schedule should be diligent, given the potential higher risk of progression, development of regional or distant metastases and death of this group compared with patients with low-risk disease. During monitoring, if repeat non-MRI-based systematic biopsies reveal > 3 positive cores or maximum CI > 50%/core of ISUP grade group 2 disease, patients should be reclassified (i.e., actively treated). For patients with a life expectancy of less than ten years, and not suitable for curative treatment, WW is a valid option and should be discussed with the patient.

6.3.2.2 Radical prostatectomy

Patients with intermediate-risk PCa should be informed about the results of two RCTs (SPCG-4 and PIVOT) 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 pre-planned subgroup analysis among men with intermediate-risk tumours, RP significantly reduced all-cause mortality (HR: 0.69, 95% CI: 0.49–0.98), but not death from PCa (0.50, 95% CI: 0.21–1.21) at ten years. A meta-analysis based on the findings of SPCG-4, PIVOT and ProtecT demonstrated a benefit from RP over observation with a significantly decreased risk of death of 9% and of disease progression of 43% [772]. However, no stratification by disease stages was performed. The risk of having positive LNs in intermediate-risk PCa is between 3.7–20.1% [773]. A large study only found 2.9% of LN invasion in a contemporary cohort of 6,883 patients undergoing RP and LND for intermediate risk PCa [774]. Nerve sparing surgery is discussed in Section 6.1.2.3.5.

6.3.2.3 Radiation therapy

6.3.2.3.1 Recommended IMRT/VMAT for intermediate-risk PCa

Patients suitable for ADT can be given combined IMRT/VMAT with short-term ADT (four to six months) [775-777]. The RTOG 0815 RCT demonstrated improved BFSR, metastasis free and prostate CSS with the addition of six months ADT to dose escalated RT [685]. For adjuvant RT of the pelvic lymphatics (45-50 Gy) for NCCN unfavourable intermediate risk (cN0) see Section 6.2.3.2.1 - Radiotherapy for localised high-risk PCa. For patients unsuitable (e.g., due to comorbidities) or unwilling to accept ADT (e.g., to preserve their sexual health) the recommended treatment is IMRT/VMAT (76–78 Gy or equivalent moderate HFX) or a combination of IMRT/VMAT and BT as described below (see Section 6.2.2.3.2). A secondary analysis of the PCS III trial has suggested that patients with NCCN favourable intermediate-risk disease (see Section 4.4) can safely omit ADT if their RT dose is 76 Gy, but this is based on an unplanned subgroup analysis and only 138 patients had favourable intermediate-risk disease. An individual discussion between the physician and the patient of the possible benefits and harms of omitting ADT in this group is essential [778].

6.3.2.3.2 Brachytherapy for intermediate-risk PCa

Systematic review recommends LDR BT monotherapy can be offered to patients with NCCN favourable intermediate-risk disease and good urinary function (see Section 4.4) [779]. Fractionated HDR BT as monotherapy can be offered to selected patients with intermediate-risk PCa although they should be informed that results are only available from small series in very experienced centres. Five-year PSA control rates over 90% are reported, with late grade 3+ GU toxicity rates < 5% and no, or very minimal, grade 3+ GI toxicity rates [728]. There are no direct data to inform on the use of ADT in this setting. Trimodality therapy with IMRT plus BT boost and short-term ADT can be considered for NCCN unfavourable intermediate-risk PCa (see Section 4.4) but patients should be made aware that the potential improvements in biochemical control are accompanied with an increased risk of long-term urinary problems [717, 719, 724].

6.3.2.4 Other options for the primary treatment of intermediate-risk PCa (experimental therapies)

6.3.2.4.1 Focal therapy

A prospective study on focal therapy using HIFU in patients with localised intermediate-risk disease was published but the data was derived from an uncontrolled single-arm case series [750]. There is a paucity of high-certainty data for either whole-gland or focal ablative therapy in the setting of intermediate-risk disease. Consequently, neither whole-gland ablative treatment nor focal treatment can be considered as standard therapy for intermediate-risk patients and, if offered, it should only be in the setting of clinical trials or prospective registries [736].

6.3.2.4.2 Androgen deprivation therapy monotherapy

Data regarding the use of ADT monotherapy for intermediate-risk disease have been inferred indirectly from the EORTC 30891 trial, which was a RCT comparing deferred ADT vs. immediate ADT in 985 patients with T0–4 N0–2 M0 disease [773]. The trial showed a small, but statistically significant, difference in OS in favour of immediate ADT monotherapy but there was no significant difference in CSS, predominantly because the risk of cancer-specific mortality was low in patients with PSA < 8 ng/mL. Consequently, the use of ADT monotherapy for this group of patients is not considered as standard, even if they are not eligible for radical treatment.

*6.3.2.5 Guidelines for the treatment of intermediate-risk disease**

Recommendations	**Strength rating**
Watchful Waiting (WW)	
Offer WW in asymptomatic patients with life expectancy < ten years (based on comorbidities and age).	Strong
Active surveillance (AS)	
Offer AS to selected patients with ISUP grade group 2 disease (e.g. < 10% pattern 4, PSA < 10 ng/mL, ≤ cT2a, low disease extent on imaging and low extent of tu-mour in biopsies (≤ 3 positive cores with Gleason score 3+4 and ≤ 50% cancer involvement/core), or another single element of intermediate-risk disease with low disease extent on imaging and low biopsy extent, accepting the potential increased risk of metastatic progression.	Weak
Patients with ISUP grade group 3 disease should be excluded from AS protocols.	Strong
Re-classify patients with low-volume ISUP grade group 2 disease included in AS protocols, if repeat non-MRI-based systematic biopsies performed during moni-toring reveal > 3 positive cores or maximum CI > 50%/core of ISUP grade group 2 disease.	Weak
Radical prostatectomy (RP)	
Offer RP to patients with a life expectancy of > ten years.	Strong
Radical prostatectomy can be safely delayed for at least three months.	Weak
Offer nerve-sparing surgery to patients with a low risk of extra-capsular disease on that side.	Strong

Radiotherapeutic treatment	
Offer low-dose rate (LDR) brachytherapy to patients with good urinary function and NCCN favourable intermediate-risk disease.	Strong
Offer intensity-modulated radiotherapy (IMRT)/volumetric modulated arc therapy (VMAT) plus image-guided radiotherapy (IGRT), with a total dose of 76–78 Gy or moderate hypofractionation (60 Gy/20 fx in 4 weeks or 70 Gy/28 fx in 6 weeks), in combination with short-term androgen deprivation therapy (ADT) (four to six months).	Strong
Offer focal boosting to MRI-defined dominant intra-prostatic tumour when using conventionally fractionated IMRT/IGRT (1.8-2.0 Gy per fraction) ensuring that Organ at Risk constraints are not exceeded	Weak
Offer ultra-hypofractionated IMRT/IGRT or SBRT, using either 36.25 Gy (40 Gy to prostate) in 5 fx or 42.7 Gy in 7 fx delivered alternate days.	Weak
Offer LDR brachytherapy boost combined with IMRT/VMAT plus IGRT to pa-tients with good urinary function and NCCN unfavourable intermediate-risk disease, in combination with short-term ADT (four to six months).	Weak
Offer high-dose rate (HDR) brachytherapy boost combined with IMRT/VMAT plus IGRT to patients with good urinary function and NCCN unfavourable in-termediate-risk disease, in combination with short-term ADT (four to six months).	Weak
Other therapeutic options	
Only offer whole-gland ablative therapy (such as cryotherapy, high-intensity focused ultrasound, etc.) or focal ablative therapy within clinical trials or registries.	Strong
Do not offer ADT monotherapy to asymptomatic men not able to receive any local treatment.	Weak

**All recommendations are based on conventional imaging with isotope bone scan and CT/MR abdomen/pelvis.*

*6.3.3 **Treatment of high-risk localised disease***

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 [780]. 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 [781]. There is no consensus regarding the optimal treatment of men with high-risk PCa.

Some evidence suggests that radical treatment for high-risk PCa can be delayed up to three months after the diagnosis without any oncological consequences [782, 783]. Systematic reviews suggest that there is a higher risk of biochemical recurrence and worse pathological outcomes when definitive treatment is given beyond a 6 to 9 months delay. However, there is no conclusive data regarding stronger endpoints (CSS or OS).

6.3.3.1 Radical prostatectomy

Provided that the tumour is not fixed to the pelvic wall or there is no invasion of the urethral sphincter, RP is a standard option in selected patients with a low tumour volume. ePLND provides accurate LN staging. Pre-operative PSMA-PET/CT is more accurate for staging generally, but can miss smaller LNs (especially LNs <5mm). ePLND may also miss LN metastasis [539, 784]. Risks and benefits of pelvic LN dissection vs. PSMA PET/CT should be discussed with the patient pre-operatively. Patients should be aware pre-operatively that surgery may be part of multi-modal treatment, with adjuvant or SRT or ADT. Neoadjuvant therapy using ADT with or without new generation HT or docetaxel is not indicated. (See Section 6.1.2.2.4) [785, 786]. Nerve sparing management is discussed in Section 6.1.2.3.5.

At 15 years follow-up cN0 patients who undergo RP but who were found to have pN1 were reported to have an overall CSS and OS of 45% and 42%, respectively [787, 788]. A SR has reported 10-year BCR-free, CSS, and OS rates ranging from 28% to 56%, 72% to 98%, and 60% to 87.6%, respectively, in pN1 patients [789]. These findings highlight that pN1 patients represent a very heterogeneous patient group and further treatment must be individualised based on risk factors (see Sections 6.2.5.2 and 6.2.5.6).

6.3.3.2 External beam radiation therapy

For high-risk localised PCa, a combined modality approach should be used consisting of IMRT/VMAT plus long-term ADT. The duration of ADT has to take into account PS, comorbidities and the number of poor prognostic factors. It is important to recognise that in several studies EBRT plus short-term ADT did not improve OS in high-risk localised PCa and long-term ADT (at least 2 to 3 years) is currently recommended for these patients [677, 678, 689]. Moderate HFX is an option in selected high-risk patients with localised disease. The CHHiP study included 12% high-risk patients (n = 386) but limited entry to those with a PSA < 30 ng/mL and a Roach formula

risk of SV involvement < 30% [661]. Patients were ineligible if they had both T3a tumours and ISUP grade group 4 or higher.

6.3.3.2.1 Lymph node irradiation in cN0

There is no clear evidence for prophylactic irradiation of the pelvic LNs in intermediate- and high-risk disease. The long-term results of the NRG/RTOG 9413-trial which randomised intermediate-risk and high-risk localised PCa patients (1,322 cN0 patients were enrolled), showed that neoadjuvant HT plus whole pelvic RT improved PFS only compared with neoadjuvant ADT plus prostate RT and whole pelvic RT plus adjuvant ADT [790]. However, at the increased risk of ≥ grade 3 GI-toxicity.

A well-conducted single-centre RCT randomised 224 patients comparing prostate-only RT (PORT) vs. whole pelvic RT (WPRT) in localised high-risk- and locally-advanced tumours (cN0) with a risk of > 20% of positive nodes (Roach formula). With a median follow-up of 68 months there was a significant improvement of distant MFS (95.9% vs. 89.2%, HR: 0.35, p = 0.01) and DFS (89.5% vs.77.2%, p = 0.02). However, there was a significant higher rate of late GU ≥ 2 effects (17.7% vs. 7.5%, p = 0.02), the trial was relatively small in size with additional limitations and these findings are therefore insufficient to define a change in practice [791, 792]. The benefits of pelvic nodal irradiation using IMRT/VMAT merit further investigation in large scale RCTs as conducted by the RTOG or the UK National Cancer Research Institute (NCRI).

6.3.3.2.2 Brachytherapy boost

In men with NCCN unfavourable intermediate- or high-risk PCa, BT boost with supplemental EBRT and HT may be considered. See Sections 6.1.3.4.1 and 6.1.3.4.2 for details on RCTs comparing EBRT alone and EBRT with LDR or HDR boost, respectively.

6.3.3.3 Options other than surgery or radiotherapy for the primary treatment of localised PCa

Currently there is a lack of evidence supporting any other treatment option apart from RP and radical RT in localised high-risk PCa. The use of ADT monotherapy was addressed by the EORTC 30891 trial [773] (see Section 6.2.4.4.2). Immediate ADT may only benefit patients with a PSA-DT < twelve months, and either a PSA > 50 ng/mL or a poorly-differentiated tumour [773, 793].

*6.3.3.4 Guidelines for radical and palliative treatment of high-risk localised disease**

Recommendations	Strength rating
Watchful Waiting (WW)	
Offer WW to asymptomatic patients with life expectancy < ten years.	Strong
Radical prostatectomy (RP)	
Offer RP to selected patients as part of potential multi-modal therapy.	Weak
Extended pelvic lymph node dissection (ePLND)	
In patients undergoing a lymph node dissection you should perform an extended PLND.	Strong
Do not perform a frozen section of nodes during RP to decide whether to proceed with, or abandon, the procedure (see Section 6.2.4.1).	Strong
Radiotherapeutic treatment	
Offer patients intensity-modulated radiation therapy (IMRT)/volumetric modu-lated arc therapy (VMAT) plus image-guided radiation therapy (IGRT) with 76–78 Gy in combination with long-term androgen deprivation therapy (ADT) (2 to 3 years).	Strong
Offer focal boosting to MRI-defined dominant intra-prostatic tumour when using normo-fractionated IMRT/IGRT (1.8-2.0 Gy per fraction) ensuring that Organ at Risk constraints are not exceeded.	Weak
Offer patients with good urinary function IMRT/VMAT plus IGRT with brachy-therapy boost (either high-dose rate or low-dose rate), in combination with long-term ADT (2 to 3 years).	Weak
Therapeutic options outside surgery or radiotherapy	
Do not offer either whole gland or focal therapy.	Strong
Only offer ADT monotherapy to those patients unwilling or unable to receive any form of local treatment if they have a prostate-specific antigen (PSA)-doubling time < twelve months, and either a PSA > 50 ng/mL or a poorly-differentiated tumour.	Strong

**All recommendations are based on conventional imaging with isotope bone scan and CT/MR abdomen/pelvis.*

6.3.4 *Treatment of locally-advanced PCa*

In the absence of high-level evidence, a SR could not define the most optimal treatment option [794]. Randomised controlled trials are only available for EBRT. A local treatment combined with a systemic treatment provides the best outcome, provided the patient is fit enough to receive both. The initial results of the SCPG-15 trials suggested that randomisation between surgery and EBRT is feasible, but oncologic outcomes are awaited [795].

6.3.4.1 *Radical prostatectomy*

Surgery for locally-advanced disease as part of a multi-modal therapy has been reported [781, 796, 797]. However, the comparative oncological effectiveness of RP as part of a multi-modal treatment strategy vs. upfront EBRT with ADT for locally-advanced PCa remains unknown, although a prospective phase III RCT (SPCG-15) comparing RP (with or without adjuvant or salvage EBRT) against primary EBRT and ADT among patients with locally-advanced (T3) disease is currently recruiting [798]. Data from retrospective case series demonstrated over 60% CSS at 15 years and over 75% OS at ten years [781, 796, 797, 799-802]. For cT3b–T4 disease, PCa cohort studies showed 10-year CSS of over 87% and OS of 65% [803, 804]. The indication for RP in all previously described stages assumes the absence of clinically detectable nodal involvement (cN0), based on conventional imaging. In case of suspected positive LNs during RP (initially considered cN0) the procedure should not be abandoned since RP may have a survival benefit in these patients. Intra-operative frozen section analysis is not justified in this case [541].

6.3.4.2 *Treatment of cN1 M0 PCa*

Lymph-node metastasised PCa is an entity where options for local therapy and systemic therapies overlap. Approximately 5% to 10% of newly diagnosed PCa patients have synchronous suspected pelvic nodal metastases on conventional imaging (CT/bone scan) without bone or visceral metastases (cN1 M0 stage). Meta-analyses have shown that PSMA-PET/CT prior to primary treatment in advanced PCa detected disease outside the prostate in 32% of cases despite prior negative conventional imaging using bone scan and pelvic CT/MRI [412]. A RCT assessing PSMA-PET/CT as staging tool in high-risk PCa confirmed these findings and showed a 32% increase in accuracy compared with conventional imaging for the detection of pelvic nodal metastases [429]. Notably, more sensitive imaging also caused a stage shift with more cases classified as miN1, but with, on average, lower nodal disease burden.

The management of cN1M0 PCa is historically based on long-term ADT combined with a local treatment. The benefit of adding local treatment has been assessed in various retrospective studies, summarised in one SR [805] including five studies only [806-810]. The results of this SR were confirmed [811]. The findings of this retrospective analysis suggested an advantage in both OS and CSS after local treatment (RT or RP) combined with ADT as compared to ADT alone. Only limited evidence exists supporting RP for cN1 patients. Moschini *et al.*, compared the outcomes of 50 patients with cN+ with those of 252 patients with pN1, but cN0 at pre-operative staging. cN+ was not a significant predictor of CSS [812].

The addition of a brachytherapy boost to ADT plus EBRT was not associated with improved OS in a retrospective study of 1,650 cN1 patients after multivariable adjustment and propensity score matching [813].

The intensification of systemic treatment (abiraterone acetate, docetaxel, zoledronic acid) has been assessed in unplanned sub-group analyses from the STAMPEDE multi-arm RCT by stratifying for cN1 and M1 status [809, 814]. The analyses were balanced for nodal involvement and for planned RT use in STAMPEDE at randomisation and at analysis. Abiraterone acetate was associated with a non-significant OS improvement (HR: 0.75, 95% CI: 0.48–1.18) in non-metastatic patients (N0/N+M0), but OS data were still immature with a low number of events. Furthermore, this was an underpowered subgroup analysis and hypothesis generating at best. Moreover, subgroup analyses were performed according to the metastatic/non-metastatic status and to the nodal status (any M) without specific data for the N1M0 population (n = 369; 20% of the overall cohort). The same would apply for the docetaxel arm in the STAMPEDE trial for which no specific subgroup analysis of newly diagnosed N1M0 PCa (n = 171, 14% of the overall cohort) was performed. However, the addition of docetaxel, zoledronic acid, or their combination, did not provide any OS benefit when stratifying by M0 and N+ status.

In the AFU-GETUG 12 trial comparing the impact of docetaxel plus estramustine in addition to ADT, 29% of included high-risk non-metastatic PCa patients had a nodal involvement (pN1) at randomisation [815]. A non-significant trend towards better relapse-free survival rates was reported in the treatment arm (HR 0.66; 86 0.43–1.01) without OS benefit. A meta-analysis of docetaxel trials in N0/N1-M0 patients concluded to an 8% 4-year survival advantage for docetaxel compared with ADT alone in terms of failure-free survival without OS benefit [816]. Two RCTs from the STAMPEDE platform protocol reported on men with *de novo* high-risk/locally-

advanced M0 disease, or relapse after primary curative therapy with high-risk features. Thirty-nine percent of patients (n = 774) were N1 on conventional imaging [817]. Radiotherapy in addition to long-term ADT was administered in 71% of these patients. Given the MFS and OS benefits observed in the overall population (see Section 6.3.4.2), combined ADT (for 3 years) and additional abiraterone (for 2 years) should be a SOC in cN1 patients in addition to prostate- and WPRT.

Table 6.3.4.1: Selected studies assessing local treatment in (any cT) cN1 M0 prostate cancer patients

Study	n	Design	Study period/ follow-up	Treatment arms	Effect on survival
Bryant, *et al.* 2018 [818]	648	Retrospective (National Veterans Affairs)	2000-2015 61 mo.	ADT ± EBRT	Significant benefit for combined treatment only if PSA levels less than the median (26 ng/mL) All-cause mortality HR: 0.50 CSS, HR: 0.38
Sarkar, *et al.* 2019 [819]	741	Retrospective (National Veterans Affairs)	2000-2015 51 mo.	ADT ± local treatment (surgery or RT)	Significant benefit for RP All cause mortality HR 0.36 CSS, HR: 0.32 No statistical difference for RP vs. RT (p ≥ 0.1) All-cause mortality HR: 047 CSS, HR: 0.88
Lin, *et al.* 2015 [807]	983 before propensity score matching	Retrospective (NCDB)	2004-2006 48 mo.	ADT ± EBRT	Significant benefit for combined treatment 5-yr OS: 73% vs. 52% HR: 0.5
Tward, *et al.* 2013 [806]	1,100	Retrospective (SEER)	1988-2006 64 mo.	EBRT (n = 397) vs. no EBRT (n = 703) No information on ADT)	Significant benefit for EBRT 5-yr CSS 78% vs. 71% HR: 0.66 5-yr. OS: 68% vs. 56%, HR: 0.70
Rusthoven, *et al.* 2014 [810]	796	Retrospective (SEER)	1995-2005 61 mo.	EBRT vs. no EBRT (no information on ADT)	Significant benefit for EBRT 10-yr OS: 45% vs. 29% HR: 0.58
Seisen, *et al.* 2018 [808]	1,987	Retrospective (NCDB)	2003-2011 50 mo.	ADT ± local treatment (surgery or RT)	Significant benefit for combined treatment 5-yr OS: 78.8% vs. 49.2% HR: 0.31 No difference between RP and RT
James, *et al.* 2016 [809]	177	Unplanned sub-group analysis RCT	2005-2014 17 mo.	ADT ± EBRT	Significant benefit for combined treatment 5-yr OS: 93% vs. 71% 2-yr FFS: 81% vs 53% FFS, HR: 0.48
Elumalai *et al.* [811]	337	Retrospective 4 centres UK	2022-2019	ADT +/- EBRT	Significant benefit for combined treatment 5-yr.OS: 87% vs. 56% HR: 0.27 5-yr. BPFS: 74.1% vs. 34.2% HR: 0.33

ADT = androgen deprivation therapy; CSS = cancer-specific survival; EBRT = external beam radiotherapy; FFS = failure-free survival; HR = hazard ratio; mo = months; n = number of patients; OS = overall survival; RP = radical prostatectomy; RT = radiotherapy; yr = year.

6.3.4.3 Options other than surgery or radiotherapy for primary treatment

6.3.4.3.1 Investigational therapies

Currently cryotherapy, HIFU or focal therapies have no place in the management of locally-advanced PCa.

6.3.4.3.2 Androgen deprivation therapy monotherapy

The deferred use of ADT as single treatment modality has been answered by the EORTC 30891 trial [773]. Nine hundred and eighty-five patients with T0–4 N0–2 M0 PCa received ADT alone, either immediately or after symptomatic progression or occurrence of serious complications. After a median follow-up of 12.8 years, the OS favoured immediate treatment (HR: 1.21, 95% CI: 1.05–1.39). Surprisingly, no different disease-free or symptom-free survival was observed, raising the question of survival benefit. In locally-advanced T3–T4 M0 HSPC unsuitable for surgery or RT, immediate ADT may only benefit patients with a PSA > 50 ng/mL and a PSA-DT < twelve months or those that are symptomatic [773, 793]. The median time to start deferred treatment was 7 years. In the deferred treatment arm 25.6% of patients died without needing treatment.

*6.3.4.4 Guidelines for radical- and palliative treatment of locally-advanced disease**

Recommendations	Strength rating
Radical prostatectomy (RP)	
Offer RP to patients with cN0 disease as part of multi-modal therapy.	Weak
Extended pelvic lymph node dissection (ePLND)	
In patients undergoing a lymph node dissection you should perform an extended PLND.	Strong
Radiotherapeutic treatments	
Offer patients with cN0 disease intensity-modulated radiation therapy (IMRT)/volumetric modulated arc therapy (VMAT) plus image-guide radiation therapy in combination with long-term androgen deprivation therapy (ADT).	Strong
Offer patients with cN0 disease and good urinary function, IMRT/VMAT plus IGRT with brachytherapy boost (either high-dose rate or low-dose rate), in combination with long-term ADT.	Weak
Offer long-term ADT for at least 2 years.	Strong
Offer IMRT/VMAT plus IGRT to the prostate in combination with long-term ADT and two years of abiraterone to cN0M0 patients with ≥ 2 high-risk factors (cT3-4, Gleason ≥ 8 or PSA ≥ 40 ng/mL).	Strong
Offer IMRT/VMAT plus IGRT to the prostate plus pelvis in combination with long-term ADT and two years of abiraterone to cN1M0 patients.	Strong
Therapeutic options outside surgery or radiotherapy	
Do not offer whole gland treatment or focal treatment.	Strong

**All recommendations are based on conventional imaging with isotope bone scan and CT/MR abdomen/pelvis.*

*6.3.5 **Adjuvant treatment after radical prostatectomy***

6.3.5.1 Introduction

Adjuvant treatment is by definition additional to the primary or initial therapy with the aim of decreasing the risk of relapse, despite the apparent full control following surgery. A post-operative detectable PSA is an indication of persistent prostate cells (see Section 6.3.6). All information listed below refers to patients with a post-operative undetectable PSA.

6.3.5.2 Risk factors for relapse

Patients with ISUP grade group > 2 in combination with EPE (pT3a) and particularly those with SV invasion (pT3b) and/or positive surgical margins are at high risk of progression, which can be as high as 50% after five years [820]. Irrespective of the pT stage, the number of removed nodes [821-828], tumour volume within the LNs and capsular perforation of the nodal metastases are predictors of early recurrence after RP for pN1 disease [829]. A LN density (defined as 'the percentage of positive LNs in relation to the total number of analysed/removed LNs') of over 20% was found to be associated with poor prognosis [830]. The number of involved nodes seems to be a major factor for predicting relapse [823, 824, 831]; the threshold considered is less than 3 positive nodes from an ePLND [540, 823, 831]. However, prospective data are needed before defining a definitive threshold value.

6.3.5.2.1 Biomarker-based risk stratification after radical prostatectomy

The Decipher® gene signature consists of a 22-gene panel representing multiple biological pathways and was developed to predict systemic progression after definitive treatment. A meta-analysis of five studies analysed the performance of the Decipher® Genomic Classifier (GC) test on men post-RP. The authors showed in multivariable analysis that Decipher® GC remained a statistically significant predictor of metastasis (HR: 1.30, 95% CI: 1.14–1.47, p < 0.001) per 0.1 unit increase in score and concluded that it can independently improve prognostication of patients post-RP within nearly all clinicopathologic, demographic, and treatment subgroups [832]. A SR of the evidence for the Decipher® GC has confirmed the clinical utility of this test in post-RP decision-making [833]. Further studies are needed to establish how to best incorporate Decipher® GC in clinical decision-making.

6.3.5.3 Immediate (adjuvant) post-operative external irradiation after RP (cN0 or pN0)

Four prospective RCTs have assessed the role of immediate post-operative RT (adjuvant RT [ART]) (undetectable PSA mostly defined as PSA < 0.1 ng/mL), demonstrating an advantage (endpoint, development of BCR) in high-risk patients (e.g., pT2 with positive surgical margins and ISUP grade group 3–5 or pT3/4 with- or without positive surgical margins and ISUP grade group 3–5) post-RP (Table 6.3.5.1). In the ARO 96-02 trial, 80% of the pT3/R1/GS 8–10 patients randomised to observation developed BCR within ten years [834]. It must be emphasised that PSA was undetectable at inclusion only in the ARO 96-02 trial which presents a major limitation interpreting these findings as patients with a detectable PSA would now be considered for salvage therapy rather than ART [834].

Table 6.3.5.1: Overview of all four randomised trials for adjuvant surgical bed radiation therapy after RP* (without ADT)

Study	n	Inclusion criteria	Randomisation	Definition of BCR PSA (ng/mL)	Median FU (mo)	Biochemical Progression-free survival	Overall survival
SWOG 8794 2009 [835]	431	pT3 cN0 ± involved SM	60-64 Gy vs. observation	> 0.4	152	10 yr.: 53% vs. 30% (p < 0.05)	**10 yr.: 74% vs. 66%** Median time: 15.2 vs. 13.3 yr., p = 0.023
EORTC 22911 2012 [836]	1,005	pT3 ± involved SM pN0 pT2 involved SM pN0	60 Gy vs. observation	> 0.2	127	10 yr.: 60.6% vs. 41% (p < 0.001)	**81% vs. 77% n.s.**
ARO 96-02 2014 [834]	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.**
FinnProstate Group 2019 [837]	250	pT2,R1/ pT3a	66.6 Gy vs. observation (+ SRT)	> 0.4 (in 2 successive measure-ments)	112 vs. 103 (patients alive)	10 yr.: 82% vs. 61% p < 0.001	**10 yr.: 92% vs. 87% n.s.**

**See Section 6.3.5.1 for delayed (salvage) post-radical prostatectomy external irradiation.*
BCR = biochemical recurrence; FU = follow-up; mo = months; n = number of patients; n.s. = not significant; OS = overall survival; PSA = prostate-specific antigen; RP = radical prostatectomy; SM = surgical margin; SRT = salvage radiotherapy.

6.3.5.4 Comparison of adjuvant- and salvage radiotherapy

Two retrospective matched studies (510 and 149 patients receiving ART) failed to show an advantage for MFS [838, 839]. However, both studies were underpowered for high-risk patients (pT3b/R1/ISUP grade group 4–5 PCa). In contrast to these studies, a propensity score-matched retrospective analysis of two cohorts of 366 pT3 and/or R1 patients found that compared to SRT at a PSA between 0.1 and 0.5 ng/mL, ART given at an undetectable PSA (< 0.1 ng/mL) improved all three endpoints; BCR, MFS, and OS [840].

Both approaches (ART and early SRT) together with the efficacy of adjuvant ADT are compared in three prospective RCTs: the Medical Research Council (MRC) Radiotherapy and Androgen Deprivation In Combination After Local Surgery (RADICALS) trial [841], the Trans-Tasman Oncology Group (TROG) Radiotherapy Adjuvant Versus Early Salvage (RAVES) trial [842], and the Groupe d'Etude des Tumeurs Uro- Genitales (GETUG-AFU 17) trial [843]. In addition, a pre-planned meta-analysis of all three trials has been published (Table 6.3.5.2) [844].

Two trials closed early after randomising 333/470 patients (RAVES) and 424/718 (GETUG-AFU-17) patients. RADICALS-RT included 1,396 patients with the option of subsequent inclusion in RADICALS-HT; 154/649 (24%) of patients starting in the adjuvant RT group also received neoadjuvant or adjuvant HT; 90 patients for six months/45 for 2 years/19 patients outside RADICALS-HT. From the SRT group, 61/228 (27%) received neoadjuvant or adjuvant HT for six months (n = 33) and two years (n = 13). Fifteen of these patients were treated outside the trial [841]. All men in the GETUG-AFU-17 trial (n = 424) received six months of HT. All together, 684 out of 2,153 patients received additional ADT for at least six months across both trials [844]. Radiotherapy to the pelvic lymphatics was allowed in the GETUG-AFU and in the RADICALS-RT trials.

The primary endpoint for RAVES and GETUG-AFU 17 was biochemical PFS, and for RADICALS-RT MFS. So far only PFS data has been reported, and not MFS- or OS data. With a median follow-up between 4.9 years and 6.25 years there was no statistically significant difference for biochemical PFS for both treatments in all three trials (see Table 6.2.5.2) indicating that in the majority of patients adjuvant irradiation should be avoided. Additionally, there was a significant lower rate of grade ≥ 2 GU late side effects and grade 3–4 urethral strictures in favour of early SRT; which may also be caused by the low number of patients with PSA-progression and subsequent need for early SRT at the time of analysis (40% of patients).

It is important to note that the indication for ART changed over the last ten years with the introduction of ultra-sensitive PSA-tests, favouring early SRT. Therefore many patients, randomised in these three trials (accruing 2006–2008) are not likely to benefit from ART as there is a low risk of biochemical progression (~20–30%) in, for example, pT3R0 or pT2R1-tumours. The median pre-SRT PSA in all 3 trials was 0.24 ng/mL. Therefore, patients with 'low-risk factors' of biochemical progression after RP should be closely followed up with ultra-sensitive assays and SRT should be discussed if needed as soon as PSA starts to rise, which has to be confirmed by a second PSA measurement (see Section 6.3). The proportion of patients with adverse pathology at RP (ISUP grade group 4–5 and pT3 with or without positive margins) in all three trials was low (between 10–20%) and therefore even the meta-analysis may be underpowered to show an outcome in favour of SRT [844]. In addition, the side-effect profile may have been impacted with a larger proportion of ART patients receiving treatment with older 3D-treatment planning techniques as compared to SRT patients (GETUG-AFU 17: ART, 69% 3D vs. 46% SRT) and patients treated more recently were more likely to undergo IMRT techniques with a proven lower rate of late side effects [634].

For these reasons, 10-year OS and MFS endpoints results should be awaited before drawing final conclusions. Due to the small number of patients with adverse pathology (ISUP grade group 4–5 and pT3) included in these three trials (between 10–20%), ART remains a recommended treatment option in highly selected patients with adverse pathology ('high-risk patients') i.e. ISUP grade group 4–5 and pT3 with or without positive margins [845, 846]. This recommendation was supported by a published retrospective multi-centre study comparing ART and SRT in patients with high-risk features (pN1 or ISUP grade group 4–5 and pT3/4-tumours) after RP [847]. After a median follow-up of 8.2 years of the 26,118 men included in the study, 2,104 patients died, 25.62% from PCa (n = 539) and 2,424 patients had adverse pathology compared with 23.694 who did not. After excluding men with persistent PSA after RP, ART when compared with early SRT showed a significantly lower acute mortality risk (p = 0.02, HR: 0.33).

Table 6.3.5.2: Overview of all three randomised trials and one meta-analysis for patients treated with adjuvant vs. early salvage RT after RP

Study	n	Inclusion criteria	Randomisation	Definition of BCR PSA (ng/mL)	Median FU (yr)	BPFS	OS or MFS	Side effects
RAVES TROG 08.03/ ANZUP 2020 [842]	333 target was 470 early closed	pT3a/pT3b any T - SM+ PSA post-RP: < 0.1 ng/mL	64 Gy ART PSA: < 0.1 ng/mL vs. 64 Gy early SRT at PSA > 0.2 ng/mL med. pre-SRT: n.r.	> 0.4 post RT	6.1	**5 yr.: 86% vs. 87%** (p > 0.05)	n.r.	LT grade ≥ GU: 70% vs. 54% (p = 0.002)

RADICALS-RT 2020 [841]	1,396	pT3a/ pT3b/pT4 PSA > 10 ng/mL pre-RP any T, SM+ Gleason 7-10 PSA post-RP: < 0.2 ng/mL	52.5 Gy (20 Fx) or 66 Gy (33 Fx) ART early SRT identical at PSA > 0.1 med.pre-SRT: 0.2 ng/mL	> 0.4 or 2 at any time	4.9	**5 yr.: 85% vs. 88%** (p = 0.56)	n.r.	Self-reported urinary incontinence 1 yr: 4.8 vs. 4 (p = 0.023) urethral stricture grade 3/4 2 yr: 6% vs. 4% (p = 0.02)
GETUG-AFU 17 2020 [843]	424 target was 718 early closed	pT3a/pT3b/ pT4a and SM + PSA post-RP: < 0.1 ng/mL	66 Gy (ART) vs. 66 Gy early SRT at PSA 0.1 both groups: 6 mo. LHRH-A med. pre-SRT 0.24	> 0.4	6.25	**5 yr: 92% vs. 90%** (p = 0.42)	n.r.	LT grade ≥ 2 GU 27% vs. 7% (p < 0.001) ED: 28% vs. 8% (p < 0.001)
ARTISTIC-Meta-analysis 2020 [844]	2,153	see above	see above	see above	4.5	**5 yr.: 89% vs. 88%** p = 0.7	n.r.	n.r.

ART = adjuvant radiotherapy; BCR = biochemical recurrence; BPFS = biochemical progression-free survival; ED = erectile dysfunction; FU = follow-up; Fx = fraction; GU = genito-urinary; LHRH = luteinising hormonereleasing hormone; LT = late toxicity; mo = months; med = median; MFS = metastasis-free survival; n.r. = not reported; OS = overall survival; PSA = prostate-specific antigen; RP = radical prostatectomy; RT = radiotherapy; SRT = salvage radiotherapy; + = positive; yr = year.

6.3.5.5 Adjuvant systemic therapy in N0 disease

Adjuvant androgen ablation with bicalutamide 150 mg daily did not improve PFS in localised disease while it did for locally-advanced disease after RT. However, this never translated to an OS benefit [848]. A SR showed a possible benefit for PFS but not OS for adjuvant androgen ablation [786].

The TAX3501 trial comparing the role of leuprolide (18 months) with and without docetaxel (6 cycles) ended prematurely due to poor accrual. A phase III RCT comparing adjuvant docetaxel against surveillance after RP for locally-advanced PCa showed that adjuvant docetaxel did not confer any oncological benefit [849]. Consequently, adjuvant chemotherapy after RP should only be considered in a clinical trial [850].

6.3.5.6 Adjuvant treatment in pN1 disease

6.3.5.6.1 Adjuvant androgen ablation alone

The combination of RP and early adjuvant HT in pN+ PCa has been shown to achieve a 10-year CSS rate of 80% and has been shown to significantly improve CSS and OS in prospective RCTs [851, 852]. However, these trials included mostly patients with high-volume nodal disease and multiple adverse tumour characteristics and these findings may not apply to men with less extensive nodal metastases.

6.3.5.6.2 Adjuvant radiotherapy combined with ADT in pN1 disease

In a retrospective multi-centre cohort study, maximal local control with RT to the prostatic fossa appeared to be beneficial in PCa patients with pN1 after RP, treated 'adjuvantly' with continuous ADT (within six months after surgery irrespective of PSA). The beneficial impact of adjuvant RT on survival in patients with pN1 PCa was highly influenced by tumour characteristics. Men with low-volume nodal disease (< 3 LNs), ISUP grade group 2–5 and pT3–4 or R1, as well as men with 3 to 4 positive nodes were more likely to benefit from RT after surgery, while the other subgroups did not [853]. In contrast, a retrospective multi-centre study including 1,614 patients and a median follow-up of 7,02 years assessed ART + ADT. Adjuvant RT compared to SRT was associated with a decreased all-cause mortality and this reduction increased with each additional positive pelvic LN, from the first one on and the highest effect was for more than 3 positive nodes [854]. These data are in agreement with a US National Cancer Database analysis based on 5,498 patients [855]. Another US National Cancer Database study including 8,074 pN1 patients reports improved OS after ADT plus EBRT (including pelvic LNs) vs. observation and vs. ADT alone in all men with single or multiple adverse pathological features. Men without any adverse pathological features did not benefit from immediate adjuvant therapy [856].

In a SR of the literature, RT with or without ADT was associated with improved survival in men with locally-advanced disease and a higher number of positive nodes [789]. Radiotherapy to the pelvic lymphatics and the prostate fossa plus long-term ADT can be offered to patients with pN1 disease. [853, 857]. However, the optimal duration of ADT is still unkown.

6.3.5.6.3 Observation of pN1 patients after radical prostatectomy and extended lymph node dissection

Several retrospective studies and a SR addressed the management of patients with pN1 PCa at RP [789, 831, 853, 857, 858]. A subset of patients with limited nodal disease (1–2 positive LNs) showed favourable oncological outcomes and did not require additional treatment.

An analysis of 209 pN1 patients with one or two positive LNs at RP showed that 37% remained metastasis-free without need of salvage treatment at a median follow-up of 60.2 months [858]. Touijer *et al.*, reported their results of 369 pN1-positive patients (40 with and 329 without adjuvant treatment) and showed that higher pathologic grade group and > 3 positive LNs were significantly associated with an increased risk of BCR on multivariable analysis [831]. Biochemical-free survival rates in pN1 patients without adjuvant treatment ranged from 43% at four years to 28% at ten years [789]. Reported CSS rates were 78% at five years and 72% at ten years. The majority of these patients were managed with initial observation after surgery, had favourable disease characteristics, and 63% had only one positive node [789]. Initial observation followed by early salvage treatment at the time of recurrence may represent a safe option in selected patients with a low disease burden [789].

*6.3.5.7 Guidelines for adjuvant treatment for pN0 and pN1 disease after radical prostatectomy**

Recommendations	Strength rating
Do not prescribe adjuvant androgen deprivation therapy (ADT) to pN0 patients.	Strong
In pN0 patients with ISUP grade group 4–5 and pT3 ± positive margins, offer adjuvant intensity-modulated radiation therapy (IMRT)/volumetric modulated arc therapy (VMAT) plus image-guided radiation therapy (IGRT).	Strong
In pN1 patients, after an extended lymph node dissection, discuss three management options, based on nodal involvement characteristics: 1. Offer adjuvant ADT; 2. Offer adjuvant ADT with additional IMRT/VMAT plus IGRT; 3. Offer observation (expectant management) to a patient after eLND and ≤ 2 nodes and a PSA < 0.1 ng/mL.	Weak

**All recommendations are based on conventional imaging with isotope bone scan and CT/MR abdomen/pelvis.*

*6.3.6 **Persistent PSA after radical prostatectomy***

Between five and 20% of men continue to have detectable or persistent PSA after RP (when defined in the majority of studies as detectable post-RP PSA of ≥ 0.1 ng/mL within 4 to 8 weeks of surgery) [859, 860]. It may result from persistent local disease, pre-existing metastases or residual benign prostate tissue.

6.3.6.1 Natural history of persistently elevated PSA after RP

Several studies have shown that persistent PSA after RP is associated with more advanced disease (such as positive surgical margins, pathologic stage ≥ T3a, positive nodal status and/or pathologic ISUP grade group > 3) and poor prognosis. Initially defined as ≥ 0.1 ng/mL, improvements in the sensitivity of PSA assays now allow for the detection of PSA at much lower levels.

Moreira *et al.*, demonstrated that failure to achieve a PSA of less than 0.03 ng/mL within six months of surgery was associated with an increased risk of BCR and overall mortality [861, 862]. However, since the majority of the published literature is based on the 0.1 ng/mL PSA cut-off, there is significantly more longterm data for this definition. Predictors of PSA persistence were higher BMI, higher pre-operative PSA and ISUP grade group ≥ 3 [862]. In patients with PSA persistence, one and 5-year BCR-free survival were 68% and 36%, compared to 95% and 72%, respectively, in men without PSA persistence [861]. Ten-year OS in patients with and without PSA persistence was 63% and 80%, respectively.

Spratt *et al.*, confirmed that a persistently detectable PSA after RP represents one of the worst prognostic factors associated with oncological outcome [863]. Of 150 patients with a persistent PSA, 95% received RT before detectable metastasis. In a multi-variable analysis the presence of a persistently detectable PSA post-RP was associated with a 4-fold increase in the risk of developing metastasis. This was confirmed by data from Preisser *et al.*, who showed that persistent PSA is prognostic of an increased risk of metastasis and death [864]. At 15 years after RP, MFS rates, OS and CSS rates were 53.0 vs. 93.2% (p < 0.001), 64.7 vs. 81.2%

(p < 0.001) and 75.5 vs. 96.2% (p < 0.001) for persistent vs. undetectable PSA, respectively. The median follow-up was 61.8 months for patients with undetectable PSA vs. 46.4 months for patients with persistent PSA. In multivariable Cox regression models, persistent PSA represented an independent predictor for metastasis (HR: 3.59, p < 0.001), death (HR: 1.86, p < 0.001) and cancer-specific death (HR: 3.15, p < 0.001).

However, not all patients with persistent PSA after RP experience disease recurrence. Xiang *et al.*, showed a 50% 5-year BCR-free survival in men who had a persistent PSA level > 0.1 but ≤ 0.2 ng/mL at 6–8 weeks after RP [865].

Rogers *et al.*, assessed the clinical outcome of 160 men with a persistently detectable PSA level after RP [866]. No patient received adjuvant therapy before documented metastasis. In their study, 38% of patients had no evidence of metastases for ≥ 7 years while 32% of the patients were reported to develop metastases within 3 years. Noteworthy is that a significant proportion of patients had low-risk disease. In multi-variable analysis the PSA slope after RP (as calculated using PSA levels 3 to twelve months after surgery) and pathological ISUP grade group were significantly associated with the development of distant metastases.

6.3.6.2 Imaging in patients with persistently elevated PSA after RP

Standard imaging with bone scan and MRI has a low detection rate in men with a PSA below 2 ng/mL. However, PSMA PET/CT has been shown to identify residual cancer with positivity rates of 33%, 46%, 57%, 82%, and 97%, in men with post-RP PSA ranges of 0–0.19, 0.2–0.49, 0.5–0.99, 1–1.99, and ≥ 2 ng/mL, respectively [867-872] which can guide SRT planning [873]. Based on these post-RP PSA ranges, Schmidt-Hegemann *et al.*, studied 129 patients who had either persistent PSA (52%) or BCR (48%) after RP, showing that men with a persistent PSA had significantly more pelvic nodal involvement on PSMA PET/CT than those developing a detectable PSA [874]. In a multi-centre retrospective study including 191 patients, ^{68}Ga-PSMA localised biochemical persistence after RP in more than two-thirds of patients with high-risk PCa features. The obturator and presacral or mesorectal nodes were identified as high risk for residual disease [875]. Another retrospective study included 150 patients with persistent PSA after RARP who were re-staged with both ^{68}Ga-PSMA and ^{18}F-DCFPyL PSMA. The authors found that in the presence of persistent PSA the majority of patients already had metastatic pelvic LNs or distant metastases which would support a role of PSMA PET/ CT imaging in guiding (salvage) treatment strategies [876]. At present there is uncertainty regarding the best treatment if PSMA PET/CT shows metastatic disease outside the pelvis.

6.3.6.3 Impact of post-operative RT and/or ADT in patients with persistent PSA

The benefit of SRT in patients with persistent PSA remains unclear due to a lack of RCTs, however, it would appear that men with a persistent PSA do less well than men with BCR undergoing RT.

Preisser *et al.*, compared oncological outcomes of patients with persistent PSA who received SRT vs. those who did not [864]. In the subgroup of patients with persistent PSA, after 1:1 propensity score matching between patients with SRT vs. no RT, OS rates at ten years after RP were 86.6 vs. 72.6% in the entire cohort (p < 0.01), 86.3 vs. 60.0% in patients with positive surgical margin (p = 0.02), 77.8 vs. 49.0% in pT3b disease (p < 0.001), 79.3 vs. 55.8% in ISUP grade group 1 disease (p < 0.01) and 87.4 vs. 50.5% in pN1 disease (p < 0.01), respectively. Moreover, CSS rates at ten years after RP were 93.7 vs. 81.6% in the entire cohort (p < 0.01), 90.8 vs. 69.7% in patients with positive surgical margin (p = 0.04), 82.7 vs. 55.3% in pT3b disease (p < 0.01), 85.4 vs. 69.7% in ISUP grade group 1 disease (p < 0.01) and 96.2 vs. 55.8% in pN1 disease (p < 0.01), for SRT vs. no RT, respectively. In multivariable models, after 1:1 propensity score matching, SRT was associated with lower risk of death (HR: 0.42, p = 0.02) and lower cancer-specific death (HR: 0.29, p = 0.03). These survival outcomes in patients with persistent PSA who underwent SRT suggest they benefit but outcomes are worse than for men experiencing BCR [877].

It is clear from a number of studies that poor outcomes are driven by the level of pre-RT PSA, the presence of ISUP grade group ≥ 4 in the RP histology and pT3b disease [878-883]. Fossati *et al.*, suggested that only men with a persistent PSA after RP and ISUP grade group ≤ 3 benefit significantly [884], although this is not supported by Preisser *et al.* [864]. The current data do not allow making any clear treatment decisions.

Addition of ADT may improve PFS [879]. Choo *et al.*, studied the addition of 2-year ADT to immediate RT to the prostate bed in patients with pT3 and/or positive surgical margins after RP [879]. Twenty-nine of the 78 included patients had persistently detectable post-operative PSA. The relapse-free rate was 85% at five years and 68% at 7 years, which was superior to the 5-year progression-free estimates of 74% and 61% in the post-operative RT arms of the EORTC and the SWOG studies, respectively, which included patients with undetectable PSA after RP [835, 836]. Patients with persistently detectable post-operative PSA comprised approximately 50% and 12%, respectively, of the study cohorts in the EORTC and the SWOG studies.

In the ARO 96-02, a prospective RCT, 74 patients with PSA persistence (20%) received immediate SRT only (66 Gy per protocol [arm C]). The 10-year clinical relapse-free survival was 63% [878]. The GETUG-22 trial comparing RT with RT plus short-term ADT for post-RP PSA persistence (0.2–2.0 ng/mL) reported good tolerability of the combined treatment. The oncological endpoints are yet to be published [885].

Two SRs addressing persistent PSA confirmed a strong correlation of PSA persistence with poor oncologic outcomes [859, 860]. Ploussard *et al.*, also reported that SRT was associated with improved survival outcomes, although the available evidence is of low quality [860].

6.3.6.4 Conclusion

The available data suggest that patients with PSA persistence after RP may benefit from early aggressive multi-modality treatment, however, the lack of prospective RCTs makes firm recommendations difficult.

6.3.6.5 Recommendations for the management of persistent PSA after radical prostatectomy

Recommendations	Strength rating
Offer a prostate-specific membrane antigen (PSMA) positron emission tomography/ computed tomography (PET/CT scan to men with a persistent prostate-specific antigen (PSA) > 0.2 ng/mL if the results will influence subsequent treatment decisions.	Weak
Treat men with no evidence of metastatic disease with salvage radiotherapy and additional hormonal therapy.	Weak

6.4 Management of PSA-only recurrence after treatment with curative intent

Follow-up will be addressed in Chapter 7 and is not discussed in this section.

*6.4.1 **Background***

Between 27% and 53% of all patients undergoing RP or RT develop a rising PSA (PSA recurrence). Whilst metastatic progression is universally preceded by rising PSA levels, physicians must inform the patient that the natural history of PSA-only recurrence may be prolonged and that a measurable PSA may not necessarily lead to clinically apparent metastatic disease. Physicians treating patients with PSA-only recurrence face a difficult set of decisions in attempting to delay the onset of metastatic disease and death while avoiding overtreating patients whose disease may never affect their OS or QoL. It should be emphasised that the treatment recommendations for these patients should be given after discussion in a multi-disciplinary team.

6.4.1.1 PSA velocity and doubling time

Various PSA kinetics definitions have been proposed with different methods of calculation (log transformed or not) and eligible PSAs:

- PSA velocity (PSAV): absolute annual increase in serum PSA (ng/mL/year);
- PSA doubling time (PSA-DT): which measures the exponential increase in serum PSA over time.

Prostate-specific antigen velocity is more simple to calculate by subtracting the initial value from the final value, dividing by time. However, by ignoring middle values, not all PSA values are accurately taken into account.

Prostate-specific antigen-DT is calculated assuming an exponential rise in serum PSA. The formula takes into account the natural logarithm of 2 divided by the slope obtained from fitting a linear regression of the natural log of PSA over time [886]. However, many different PSA-DT calculations have been assessed according to the mathematical formula used and to the included PSA values (number, time period, intervals) [887]. For example, the 'MSKCC' method calculates a regression slope integrating all PSA values. Other methods transform PSA before calculating the slope and do not include all PSA values (different time frames and minimal intervals) [888]. O'Brien and colleagues identified more than 20 different definitions of PSAV and PSA-DT and demonstrated that obtained values could vary widely between definitions [888].
However, some rules can be considered for PSA-DT calculation [886]:

- At least 3 PSA measurements are required;
- A minimum time period between measurements (4 weeks) is preferable due to potential
- statistical 'noise' when PSA values are obtained too close together (this statement can be
- reconsidered in case of very active disease);
- All included PSA values should be obtained within the past twelve months at most, to reflect the current disease activity;
- PSA-DT is often mentioned in months, or in weeks in very active disease.

These measurements do not provide additional information compared with PSA alone [479, 888-890]. In the post-local therapy relapse setting, PSA-DT has been correlated with distant progression and with poorer outcomes after salvage treatments [891, 892]. Prostate-specific antigen-DT has been linked with metastasis-free- and OS in non-metastatic CRPC (nmCRPC) and identifies patients with high-risk nmCRPC who benefit from intensified therapy (PSA-DT threshold < ten months) [893].

6.4.2 Controversies in the definitions of clinically relevant PSA relapse

The PSA level that defines treatment failure depends on the primary treatment. Patients with rising PSA after RP or primary RT have different risks of subsequent symptomatic metastatic disease based on various parameters, including the PSA level. Therefore, physicians should carefully interpret BCR endpoints when comparing treatments. Clinicians should interpret a PSA rise in light of the EAU BCR risk groups (see Section 6.3.3).

After RP, the threshold that best predicts further metastases is a PSA > 0.4 ng/mL and rising [894-896]. However, with access to ultra-sensitive PSA testing, a rising PSA much below this level will be a cause for concern for patients.

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% for clinical failure) is 'any PSA increase > 2 ng/mL higher than the PSA nadir value, regardless of the serum concentration of the nadir' [897].

After HIFU or cryotherapy no endpoints have been validated against clinical progression or survival; therefore, it is not possible to give a firm recommendation of an acceptable PSA threshold after these alternative local treatments [898].

6.4.3 Natural history of biochemical recurrence

Once a PSA recurrence has been diagnosed, it is important to determine whether the recurrence has developed at local or distant sites. A SR and meta-analysis investigated the impact of BCR on clinical endpoints and concluded that patients experiencing BCR are at an increased risk of developing distant metastases, PCa-specific and overall mortality [898]. However, the effect size of BCR as a risk factor for mortality is highly variable. After primary RP its impact ranges from HR 1.03 (95% CI: 1.004–1.06) to HR 2.32 (95% CI: 1.45–3.71) [899, 900]. After primary RT, OS rates are approximately 20% lower at eight to ten years follow-up even in men with minimal co-morbidity [901, 902]. Still, the variability in reported effect sizes of BCR remains high and suggests that only certain patient subgroups with BCR might be at an increased risk of mortality.

The risk of subsequent metastases, PCa-specific- and overall mortality may be predicted by the initial clinical and pathologic factors (e.g., T-category, PSA, ISUP grade group) and PSA kinetics (PSA-DT and interval to PSA failure), which was further investigated by the SR [898].

For patients with BCR after RP, the following outcomes were found to be associated with significant prognostic factors:

- distant metastatic recurrence: positive surgical margins, high RP specimen pathological ISUP grade group, high pT category, short PSA-DT, high pre-SRT PSA;
- prostate-cancer-specific mortality: high RP specimen pathological ISUP grade group, short interval to biochemical failure as defined by investigators, short PSA-DT;
- overall mortality: high RP specimen pathological ISUP grade group, short interval to biochemical failure, high PSA-DT.

For patients with BCR after RT, the corresponding outcomes are:

- distant metastatic recurrence: high biopsy ISUP grade group, high cT category, short interval to biochemical failure;
- prostate-cancer-specific mortality: short interval to biochemical failure;
- overall mortality: high age, high biopsy ISUP grade group, short interval to biochemical failure, high initial (pre-treatment) PSA.

Based on this meta-analysis, proposal is to stratify patients into two risk categories since not all patients with BCR will have similar outcomes (see Table 6.4.1). The stratification into 'EAU Low-Risk' or 'EAU High-Risk' BCR after RP has recently been validated in a European cohort [903].

Table 6.4.1: EAU risk categories for patients developing biochemical recurrence

	EAU Low Risk BCR	EAU High Risk BCR
After RP	PSA-DT > 1 yr AND pathological ISUP grade group < 4	PSA-DT ≤ 1 yr OR pathological ISUP grade group 4–5
After RT	interval to biochemical failure > 18 mo AND biopsy ISUP grade group < 4	interval to biochemical failure ≤ 18 mo OR biopsy ISUP grade group 4–5

*6.4.4 **The role of imaging in PSA-only recurrence***

Imaging is only of value if it leads to a treatment change which results in an improved outcome. In practice, however, there are very limited data available regarding the outcome's consequent on imaging at recurrence.

6.4.4.1 Assessment of metastases (including nodal)

6.4.4.1.1 Bone scan and abdominopelvic CT

Because BCR after RP or RT precedes clinical metastases by seven to eight years on average [825, 904], the diagnostic yield of conventional imaging techniques (bone scan and abdominopelvic CT) is low in asymptomatic patients [905]. In men with PSA-only recurrence after RP the probability of a positive bone scan is < 5%, when the PSA level is < 7 ng/mL [906, 907]. Only 11–14% of patients with BCR after RP have a positive CT [906]. In a series of 132 men with BCR after RP the mean PSA level and PSA velocity associated with a positive CT were 27.4 ng/mL and 1.8 ng/mL/month, respectively [908].

6.4.4.1.2 Choline PET/CT

In two different meta-analyses the combined sensitivities and specificities of choline PET/CT for all sites of recurrence in patients with BCR were 86–89% and 89–93%, respectively [909, 910]. Choline PET/CT may detect multiple bone metastases in patients showing a single metastasis on bone scan [911] and may be positive for bone metastases in up to 15% of patients with BCR after RP and negative bone scan [912]. The specificity of choline PET/CT is also higher than bone scan, with fewer false positive and indeterminate findings [416]. Detection of LN metastases using choline PET/CT remains limited by the relatively poor sensitivity of the technique (see Section 5.3.2.3). Choline PET/CT sensitivity is strongly dependent on the PSA level and kinetics [424, 913, 914]. In patients with BCR after RP, PET/CT detection rates are only 5–24% when the PSA level is < 1 ng/mL but rise to 67–100% when the PSA level is > 5 ng/mL. Despite its limitations, choline PET/CT may change medical management in 18–48% of patients with BCR after primary treatment [915-917].

Choline PET/CT should only be recommended in patients fit enough for curative loco-regional salvage treatment.

6.4.4.1.3 Fluoride PET/CT

^{18}F-NaF PET/CT has a higher sensitivity than bone scan in detecting bone metastases [918]. However, ^{18}F -NaF PET/CT is limited by a relative lack of specificity and by the fact that it does not assess soft-tissue metastases [919].

6.4.4.1.4 Fluciclovine PET/CT

^{18}F-Fluciclovine PET/CT has been approved in the U.S. and Europe and it is therefore one of the PCa-specific radiotracers widely commercially available [919-922].

^{18}F-Fluciclovine PET/CT has a slightly higher sensitivity than choline PET/CT in detecting the site of relapse in BCR [923]. In a multi-centre trial evaluating 596 patients with BCR in a mixed population, fluciclovine PET/CT showed an overall detection rate of 67.7%; lesions could be visualised either at local level (38.7%) or in pelvic LNs (32.6%) [924]. As for choline PET/CT, fluciclovine PET/CT sensitivity is dependent on the PSA level, with a sensitivity likely inferior to 50% at PSA level < 1 ng/mL.

In a prospective RCT evaluating the impact of ^{18}F-fluciclovine PET/CT on SRT management decisions in patients with recurrence post-prostatectomy, in 28 of 79 (35.4%) patients overall radiotherapeutic management changed following ^{18}F-fluciclovine PET/CT [925]. ^{18}F-Fluciclovine PET/CT had a significantly higher positivity rate than conventional imaging (abdominopelvic CT or MRI plus bone scan) for whole body (79.7% vs. 13.9%, p < 0.001), prostate bed (69.6% vs. 5.1%, p < 0.001), and pelvic LNs (38.0% vs. 10.1%, p < 0.001) [925]. However, as yet, no data demonstrating that these changes translate into a survival benefit are available.

6.4.4.1.5 Prostate-specific membrane antigen based PET/CT

PSMA PET/CT has shown good potential in patients with BCR, although most studies are limited by their retrospective design. Reported predictors of ^{68}Ga-PSMA PET in the recurrence setting were updated based on a high-volume series (see Table 6.4.2) [867]. High sensitivity (75%) and specificity (99%) were observed on per-lesion analysis.

Table 6.4.2: PSMA-positivity separated by PSA level category [867]

PSA (ng/mL)	^{68}Ga-PMSA PET positivity
< 0.2	33% (CI: 16–51)
02–0.49	45% (CI: 39–52)
0.5–0.99	59% (CI: 50–68)
1.0–1.99	75% (CI: 66–84)
2.0+	95% (CI: 92–97)

PSA = prostate-specific antigen; ^{68}Ga-PSMA PET = Gallium-68 prostate-specific membrane antigen positron emission tomography.

PSMA PET/CT seems substantially more sensitive than choline PET/CT, especially for PSA levels < 1 ng/mL [926, 927]. In a study of 314 patients with BCR after treatment and a median PSA level of 0.83 ng/mL, ^{68}Ga-PSMA PET/CT was positive in 197 patients (67%) [928]. In another prospective multi-centre trial including 635 patients with BCR after RP (41%), RT (27%), or both (32%), PPV for ^{68}Ga-PSMA PET/CT was 0.84 (95% CI: 0.75–0.90) by histopathologic validation (primary endpoint, n = 87) and 0.92 (95% CI: 0.75–0.90) by a composite reference standard. Detection rates significantly increased with PSA value [929].

A prospective multi-centre, multi-reader, open-label, phase II/III trial (OSPREY) evaluated the diagnostic performance of ^{18}F-DCFPyL in patients with presumptive radiologic evidence of recurrent or metastatic PCa on conventional imaging [837]. Median sensitivity and median PPV were 95.8% (95% CI: 87.8%–99.0%) and 81.9% (95% CI: 73.7%–90.2%), respectively.

Another prospective study evaluated the diagnostic performance of 18F-DCFPyL in 208 men with BCR after RP or RT. The primary endpoint, the correct localisation rate was achieved, demonstrating positive findings on 18F-DCFPyL PET/CT in the setting of negative standard conventional imaging [930]. At present there are no conclusive data about comparison of such tracers [931].

A prospective, open label, cross-over study, the PYTHON trial, has compared the per-patient detection rates (DR) of ^{18}F-DCFPyL versus 18F-fluoromethylcholine PET/CT, in biochemical recurrence (BCR) setting. A total of 201 high-risk PCa patients with first BCR after radical prostatectomy or radiation therapy have completed the study. The per-patient DR was significantly higher for ^{18}F-DCFPyL compared to ^{18}F-fluoromethylcholine PET/CT (58% (117/201 patients) vs. 40% (81/201 patients), p < 0.0001). DR increased with higher PSA values for both tracers (PSA ≤ 0.5 ng/ml: 26/74 (35%) vs. 22/74 (30%); PSA 0.5 to ≤ 1.0 ng/ml: 17/31 (55%) vs. 10/31 (32%); PSA 1.01 to < 2.0 ng/ml: 13/19 (68%) vs. 6/19 (32%);PSA > 2.0: 50/57 (88%) vs. 39/57 (68%) for ^{18}FDCFPyL- and ^{18}F-fluoromethylcholine -PET/CT, respectively) [932]. Comparable results were found in a phase III trial of ^{18}F-PSMA-1007 versus 18F-Fluorocholine PET/CT for the localisation of prostate cancer biochemical recurrence. In this prospective, randomised, crossover multi-centre study, the overall correct detection rates were significantly higher for ^{18}F-PSMA-1007 than for ^{18}F-fluorocholine when undetermined findings were considered positive for malignancy (0.82 vs. 0.65; p < 0.0001) [933].

6.4.4.1.6 Whole-body and axial MRI

Whole body MRI has not been widely evaluated in BCR because of its limited value in the detection of early metastatic involvement in normal-sized LNs [414, 427, 934]. In a prospective series of 68 patients with BCR, the diagnostic performance of DW-MRI was significantly lower than that of ^{68}Ga-PSMA PET/CT and ^{18}NaF PET/CT for diagnosing bone metastases [935].

6.4.4.2 Assessment of local recurrences

6.4.4.2.1 Local recurrence after radical prostatectomy

Because the sensitivity of anastomotic biopsies is low, especially for PSA levels < 1 ng/mL [905], SRT is usually decided on the basis of BCR without histological proof of local recurrence. The dose delivered to the prostatic fossa tends to be uniform since it has not been demonstrated that a focal dose escalation at the site of recurrence improves the outcome. Therefore, most patients undergo SRT without local imaging.

Magnetic resonance imaging can detect local recurrences in the prostatic bed. The PSA threshold for MRI positivity seems between 0.3 and 0.5 ng/mL; PSA kinetics also influence the MRI positivity, even at low PSA values [936]. Two single-centre studies found that a negative MRI was an independent predictor of failure of SRT [937, 938]. Conversely, a small (≤0.4 cc) relapse located at the vesico-urethral anastomosis is associated with excellent prognosis at salvage RT [939]. The Prostate Imaging for Recurrence Reporting (PI-RR) system has been recently launched to standardise MRI interpretation in the context of BCR after RP or RT [940]. Initial assessment suggests good reproducibility of the score [941].

Choline PET/CT is less sensitive for local relapse than MRI but detects more regional and distant metastases [942].

The detection rates of ^{68}Ga-PSMA PET/CT in patients with BCR after RP increase with the PSA level [943]. PSMA PET/CT studies showed that a substantial part of recurrences after RP were located outside the prostatic fossa, even at low PSA levels [868, 944]. Combining ^{68}Ga-PSMA PET and MRI may improve the detection of local recurrences, as compared to ^{68}Ga-PSMA PET/CT alone [945-947].

The EMPIRE-1, a single-centre, open-label, phase II/III RCT included 365 patients with detectable PSA after RP, but negative results on conventional imaging. They were randomised to RT directed by conventional imaging alone or to conventional imaging plus ^{18}F-fluciclovine-PET/CT; patients with M1 disease in the PET/CT group (n = 4) were excluded Patients with cN1 were irradiated to the pelvic nodes, but without a boost to the metastases. After a median follow-up of 3.5 years, the PET/CT group was significantly associated with longer event-free survival (HR: 2.04, 95% CI: 1.06–3.93, p = 0.0327) [948].

6.4.4.2.2 Local recurrence after radiation therapy

In patients with BCR after RT, biopsy status is a major predictor of outcome, provided the biopsies are obtained 18–24 months after initial treatment. Given the morbidity of local salvage options it is necessary to obtain histological proof of the local recurrence before treating the patient [905].

MRI has yielded excellent results in identifying local recurrence and can be used for biopsy targeting and guiding local salvage treatment [905, 949, 950], even if it slightly underestimates the volume of the local recurrence [951]. Prostate-specific membrane antigen PET/CT can also detect local recurrences after RT [867] and concordance between PSMA PET/CT and MRI is highly suggestive of cancer recurrence [952].

6.4.4.3 Summary of evidence of imaging in case of biochemical recurrence

In patients with BCR imaging can detect both local recurrences and distant metastases, however, the sensitivity of detection depends on the PSA level. After RP, PSMA PET/CT is the imaging modality with the highest sensitivity at low PSA levels (< 0.5 ng/mL) and may help distinguishing patients with recurrences confined to the prostatic fossa from those with distant metastases which may impact the design and use of post-RP SRT. After RT, MRI has shown excellent results at detecting local recurrences and guiding prostate biopsy. Given the substantial morbidity of post-RT local salvage treatments, distant metastases must be ruled out in patients with local recurrences and who are fit for these salvage therapies. Choline-,fluciclovine- or PSMA-PET/CT can be used to detect metastases in these patients but for this indication PSMA PET/CT seems the most sensitive technique.

6.4.4.4 Summary of evidence and guidelines for imaging in patients with biochemical recurrence

Recommendations	Strength rating
Prostate-specific antigen (PSA) recurrence after radical prostatectomy	
Perform prostate-specific membrane antigen (PSMA) positron emission tomography/ computed tomography (PET/CT) if the PSA level is > 0.2 ng/mL and if the results will influence subsequent treatment decisions (EAU BCR risk groups).	Weak
In case PSMA PET/CT is not available, and the PSA level is ≥ 1 ng/mL, perform fluciclovine PET/CT or choline PET/CT imaging if the results will influence subsequent treatment decisions.	Weak
PSA recurrence after radiotherapy	
Perform prostate magnetic resonance imaging to localise abnormal areas and guide biopsies in patients fit for local salvage therapy.	Weak
Perform PSMA PET/CT (if available) or fluciclovine PET/CT or choline PET/CT in patients fit for curative salvage treatment.	Strong

6.4.5 *Treatment of PSA-only recurrences*

The timing and treatment modality for PSA-only recurrences after RP or RT remain a matter of controversy based on the limited evidence.

6.4.5.1 *Treatment of PSA-only recurrences after radical prostatectomy*

6.4.5.1.1 Salvage radiotherapy for PSA-only recurrence after radical prostatectomy (cTxcN0M0, without PET/CT)

Early SRT provides the possibility of cure for patients with an increasing PSA after RP. Boorjian *et al.*, reported a 75% reduced risk of systemic progression with SRT when comparing 856 SRT patients with 1,801 non-SRT patients [953]. The RAVES and RADICAL trials assessing SRT in post-RP patients with PSA levels exceeding 0.1–0.2 ng/mL showed 5-year freedom from BCR and BCR-free survival rates of 88% [841, 954]. Tilki *et al.* demonstrated the results of a matched pair analysis of 1832 patients with BCR, 32.9% (n = 603) received SRT without ADT, 1229 (67,1%) had a observational strategy. The median follow-up was 95.9 months. Median total SRT dose was 70.2 Gy. After 1:1 propensity score matching, at fiveteen years after RP, MFS and OS rates were 84.3 versus 76.9% (p < 0.001) and 85.3 versus 74.4% (p = 0.04) for SRT and noRT, respectively [955].

The PSA level at BCR was shown to be prognostic [953]. More than 60% of patients who are treated before the PSA level rises to > 0.5 ng/mL will achieve an undetectable PSA level [956-958], corresponding to a ~80% chance of being progression-free five years later [959]. A retrospective analysis of 635 patients who were followed after RP and experienced BCR and/or local recurrence and either received no salvage treatment (n = 397) or SRT alone (n = 160) within two years of BCR showed that SRT was associated with a 3-fold increase in PCa-specific survival relative to those who received no salvage treatment (p < 0.001). Salvage RT has been shown to be effective mainly in patients with a short PSA-DT [960].

In a retrospective multi-centre study including 25,551 patients with at most one high-risk factor after RP (ISUP grade group 4-5 or pT3/4), initiating sRT above a PSA level of 0.25 ng/mL was associated with increased ACM-risk. After a median follow-up of six years, patients who received sRT at a PSA level >0.25 ng/mL had a significantly higher ACM-risk (AHR, 1.49; 95% CI, 1.11 to 2.00; P =.008) compared with men who received sRT when the PSA was ≤0.25 mg/mL [961]. For an overview of SRT see Table 6.4.3.

The EAU BCR definitions have been externally validated and may be helpful for individualised treatment decisions [898, 903]. Despite the indication for salvage RT, a 'wait and see' strategy remains an option for the EAU BCR 'Low-Risk' group [898, 903].

Although biochemical progression is now widely accepted as a surrogate marker of PCa recurrence; metastatic disease, disease-specific and OS are more meaningful endpoints to support clinical decision-making. A SR and meta-analysis on the impact of BCR after RP reports SRT to be favourable for OS and PCSM. In particular SRT should be initiated in patients with rapid PSA kinetics after RP and with a PSA cut-off of 0.4 ng/mL [898]. An international multi-institutional analysis of pooled data from RCTs has suggested that MFS is the most valid surrogate endpoint with respect to impact on OS [962, 963]. Table 6.4.4 summarises results of recent studies on clinical endpoints after SRT.

Table 6.4.3: Selected studies of post-prostatectomy salvage radiotherapy, stratified by pre-salvage radiotherapy PSA level* (cTxcN0M0, without PET/CT)

Study	n	Median FU (mo)	pre-SRT PSA (ng/mL) median	RT dose ADT	bNED/PFS (year)	5-yr. results
Bartkowiak, *et al.* 2018 [964]	464	71	0.31	66.6 Gy	54% (5.9)	73% vs. 56%; PSA < 0.2 vs. ≥ 0.2 ng/mL p < 0.0001
Stish, *et al.* 2016 [956]	1,106	107	0.6	68 Gy 16% ADT	50% (5) 36% (10)	44% vs. 58%; PSA ≤ 0.5 vs. > 0.5 ng/mL p < 0.001
Tendulkar, *et al.* 2016 [965]	2,460	60	0.5	66 Gy 16% ADT	56% (5)	Pre-SRT PSA 71% 0.01–0.2 ng/mL 63% 0.21–0.5 ng/mL 54% 0.51–1.0 ng/mL 43% 1.01–2.0 ng/mL 37% > 2.0 ng/mL p < 0.001

Tilki *et al.* 2023 [961]	25,551 SRT at: PSA <0.25 N=1,556 PSA>0.25 N=1.677 No RT: N=21,645	72	Not given	Med. 68.4 Gy SRT+ADT:1489 ART:N= 673 ADT: 208	Not given	ACM (six years): HR 1.49 of higher risk when SRT at start was >0.25 (p=0.008)

**Androgen deprivation therapy can influence the outcome 'biochemically no evidence of disease (bNED)' or 'progression-free survival'. To facilitate comparisons, 5-year bNED/PFS read-outs from Kaplan-Meier plots are included.*

ADT = androgen deprivation therapy; bNED = biochemically no evidence of disease; FU = follow up; mo = months; n = number of patients; PFS = progression-free survival; PSA = prostate-specific antigen; SRT = salvage radiotherapy; yr = year.

Table 6.4.4: Selected studies reporting clinical endpoints after SRT (cTxcN0M0, without PET/CT) (the majority of included patients did not receive ADT)

Study	n	Median FU (mo)	Regimen	Outcome
Bartkowiak, *et al.* 2018 [964]	464	71	66.6 (59.4-72) Gy no ADT	5.9 yr. OS post-SRT PSA < 0.1 ng/mL 98% post-SRT PSA ≥ 0.1 ng/mL 92% p = 0.005
Jackson, *et al.* 2014 [966]	448	64	68.4 Gy no ADT	5 yr. DM post-SRT PSA < 0.1 ng/mL 5% post-SRT PSA ≥ 0.1 ng/mL 29% p < 0.0001 5 yr. DSM post-SRT PSA < 0.1 ng/mL 2% post-SRT PSA ≥ 0.1 ng/mL 7% p < 0.0001 OS post-SRT PSA < 0.1 ng/mL 97% post-SRT PSA ≥ 0.1 ng/mL 90% p < 0.0001
Stish, *et al.* 2016 [956]	1,106	107	68 (64.8-70.2) Gy 39% 2D treatment planning incl. 16% ADT	5 and 8.9 yr. DM SRT: PSA ≤ 0.5 ng/mL 7% and 12% SRT: PSA > 0.5 ng/mL 14% and 23% p < 0.001 5 and 8.9 yr. DSM SRT: PSA ≤ 0.5 ng/mL < 1% and 6% SRT: PSA > 0.5 ng/mL 5% and 10% p = 0.02 5 and 8.9 yr. OS SRT: PSA ≤ 0.5 ng/mL 94% and 86% SRT: PSA > 0.5 ng/mL 91% and 78% p = 0.14
Tendulkar, *et al.* 2016 [965]	2,460	60	66 (64.8-68.4) Gy incl. 16% ADT	10-yr. DM (19% all patients) Pre-SRT PSA 9% 0.01–0.2 ng/mL 15% 0.21–0.5 ng/mL 19% 0.51–1.0 ng/mL 20% 1.01–2.0 ng/mL 37% > 2.0 ng/mL p < 0.001

ADT = androgen deprivation therapy; DM = distant metastasis; DSM = disease specific mortality; FU = follow up; mo. = month; n = number of patients; OS = overall survival; PSA = prostate specific antigen; SRT = salvage radiotherapy.

6.4.5.1.2 Salvage radiotherapy combined with androgen deprivation therapy (cTxcN0, without PET/CT)

Data from RTOG 9601 suggest both CSS and OS benefit when adding two years of bicalutamide (150 mg o.d.) to SRT [967]. According to GETUG-AFU 16 also 6-months treatment with a LHRH-analogue can significantly improve 10-year BCR, biochemical PFS and, modestly, MFS. However, SRT combined with either goserelin or placebo showed similar DSS and OS rates [968]. In addition, Pollack *et al.*, reported on the results of a randomised 3-arm phase III trial (NRG Oncology/RTOG 0534 SPPORT) adding six months treatment with a LHRH-analogue to SRT of the prostate bed (PBRT) (group 2) compared with PBRT alone (group 1) or the former combination with PBRT-RT and pelvic LN RT (PLNRT) (group 3) [969]. The primary endpoint was freedom from progression (FFP) after five years. However, using the phoenix-definition of biochemical progression (nadir + 2 ng/mL used for definitive RT), and not the criterion of nadir + 0.2, as is used commonly (but without clear evidence) will have resulted in a later diagnosis of progression in the SPPORT trial.

With a median follow-up of 8.2 years of the surviving patients FFP increased significant for group 3 (87.4%) compared with group 2 (81.3%) ($p = 0.0027$) and group 1 (70.9%) ($p < 0.0001$) The difference between group 2 and group 1 was also significant ($p < 0.0001$). Distant metastasis incidence rates were lowest in group 3 and were lower compared with group 1 (PBRT only, HR: 0.52) similar to the rate of PCa deaths (HR: 0.51). No significant difference was seen for OS. There was a significantly higher risk of both acute- and late side effects in group 3. Therefore, the role of additional PLNRT remains unclear and should be further proven in RCTs including PSMA PET-CT [970]. Table 6.4.5 provides an overview of these three RCTs.

These RCTs support adding ADT to SRT. However, when interpreting these data it has to be kept in mind that RTOG 9601 used outdated radiation dosages (< 66 Gy) and technique. The question with respect to the patient risk profile, whether to offer combination treatment or not, and the optimal combination (LHRH or bicalutamide) remains, as yet, unsolved. The EAU BCR risk classification may offer guidance in this respect [898].

One of these RCTs reports improved OS (RTOG 96-01) and the other (GETUG-AFU 16) improved MFS but due to methodological discrepancies and also related to follow-up and risk, it is, as yet, not evident which patients should receive ADT, which type of ADT, and for how long. Men at high risk of further progression (e.g., with a PSA ≥ 0.7 ng/mL and GS ≥ 8) may benefit from SRT combined with two years of ADT; for those at lower risk (e.g., PSA < 0.7 ng/mL and GS = 8) SRT combined with six months of ADT may be sufficient. Men with a low-risk profile (PSA < 0.5 ng/mL and GS < 8) may receive SRT alone. In a sub-analysis of men with a PSA of 0.61 to 1.5 (n = 253) there was an OS benefit associated with antiandrogen assignment (HR: 0.61, 95% CI: 0.39–0.94) [971]. In those receiving early SRT (PSA 0.6 ng/mL, n = 389), there was no improvement in OS (HR: 1.16, 95% CI: 0.79–1.70), with increased other-cause mortality (sub-distribution HR: 1.94, 95% CI: 1.17–3.20, p = 0.01) and increased odds of late grades 3–5 cardiac and neurologic toxic side effects (OR: 3.57, 95% CI: 1.09–15.97, p = 0.05). These results suggest that pre-SRT PSA level may be a prognostic biomarker for outcomes of anti-androgen treatment with SRT. In patients receiving late SRT (PSA > 0.6 ng/mL), HT was associated with improved outcomes. In men receiving early SRT (PSA < 0.6 ng/mL), long-term anti-androgen treatment was not associated with improved OS [971].

A SR addressing the benefit from combining HT with SRT suggested risk stratification of patients based on the pre-SRT PSA (< 0.5, 0.6–1, > 1 ng/mL), margin status and ISUP grade as a framework to individualise treatment [972].

Table 6.4.5: Randomised controlled trials comparing salvage radiotherapy combined with androgen deprivation therapy vs. salvage radiotherapy alone

Study	n	Risk groups	Median FU (mo)	Regimen	Outcome
GETUG-AFU 16 2019 [968]	369 RT + ADT 374 RT	ISUP grade ≤ 2/3 89% ISUP grade ≥ 4 11% cN0	112	66 Gy PBRT + 6 mo. LHRH analogue 66 Gy BPRT	**10-yr.** **PFS: RT + ADT, 64%** **PFS: RT, 49%** p < 0.0001 **MFS: RT + ADT, 75%** **MFS: RT, 69%** p = 0.034

RTOG 9601 2017 [967]	384 RT + ADT 376 RT	pT2 R1, pT3 cN0	156	64.8 Gy PBRT + bicalutamide 24 mo. 64.8 Gy PBRT + placebo	**12-yr.** **cumulative DM** **RT + ADT: 14%** **RT + placebo: 23%** p = 0.005 **OS** **RT + ADT: 76%** **RT + placebo: 71%** p = 0.04 **DSM** **RT + ADT: 5.8%** **RT + placebo: 13.4%** p < 0.001
NRG Oncology/ RTOG 0534 SPPORT [969]	564 PBRT + alone 578 PBRT + ADT 574 PBRT + PLNRT + ADT	pT2 or pT3 ISUP < 5 Pre SRT PSA: 0.1-2.0	survivors: 8.2 years	64.8–70.2 Gy PBRT 64.8–70.2 Gy PBRT + 6 mo. LHRH analogue 64.8–70.2 Gy PBRT + 45 Gy PLNRT + 6 mo. LHRH analogue	**5-yr. FFP (primary** **endpoint)** **70.9% Group 1** **81.3% Group 2** **87.4% Group 3** **Comparisons :** **G 3 vs. G 1:** p < 0.0001 **G 2 vs. G 1** p < 0.0001 **G 3 vs. G 2** p < 0.0027

ADT = androgen deprivation therapy; DM = distant metastasis; DSM = disease specific mortality; PFS = progression free survival; FFP = Freedom From Progression; FU = follow-up; LHRH = luteinising hormone-releasing hormone; MFS = metastasis-free survival; OS = overall survival; PFS = progression-free survival; mo = months; n = number of patients; RT = radiotherapy; yr = year, PBRT = prostate bed radiotherapy; PLNRT = pelvic lymph node radiotherapy.

6.4.5.1.2.1 Target volume, dose, toxicity

There have been various attempts to define common outlines for 'clinical target volumes' for pN0 PCa [973, 974] and for organs at risk of normal tissue complications [973]. However, given the variations of techniques and dose-constraints, a satisfactory consensus has not yet been achieved. A benefit in biochemical PFS but not MFS has been reported in patients receiving whole pelvis SRT (± ADT) but the advantages must be weighed against possible side effects [970]. This is supported by data from the SPPORTTrial (NRG Oncology/RTOG 0534 SPPORT) but it remains controversial [969].

The optimal SRT dose has not been well defined. It should be at least 64 Gy to the prostatic fossa (± the base of the SVs, depending on the pathological stage after RP) [846, 957, 975]. In a SR, the pre- SRT PSA level and SRT dose both correlated with BCR, showing that relapse-free survival decreased by 2.4% per 0.1 ng/mL PSA and improved by 2.6% per Gy, suggesting that the treatment dose above 70 Gy should be administered at the lowest possible PSA level [976]. The combination of pT stage, margin status and ISUP grade group and the PSA at SRT seems to define the risk of biochemical progression, metastasis and overall mortality [838, 977, 978]. In a study on 894 node-negative PCa patients, doses ranging from 64 to > 74 Gy were assigned to twelve risk groups defined by their pre-SRT PSA classes < 0.1, 0.1–0.2, 0.2–0.4, and > 0.4 ng/mL and ISUP grade group < 1 vs. 2/3 vs. > 4 [979]. The updated Stephenson nomograms incorporate the SRT and ADT doses as predictive factors for biochemical failure and distant metastasis [965].

Two RCT's were published (Table 6.4.6). Intensity-modulated radiation therapy plus IGRT was used in 57% of the patients in the SAKK-trial [980] and in all patients of a Chinese trial [981]. No patient had a PSMA PET/CT before randomisation. The primary endpoint in both trials was 'freedom from biochemical progression', which was not significantly improved with higher doses. However, in the Chinese trial a subgroup analysis showed a significant improvement of this endpoint for patients with Gleason 8-10 tumours (79.7% vs. 55%, p = 0.049) [981]. In this trial, patients were treated with ART or SRT and the number of patients was relatively small (n = 144). At this time it seems difficult to draw final conclusions about the optimal total RT-dose and longer follow-up should be awaited.

Table 6.4.6: Randomised trials investigating dose escalation for SRT without ADT and without PET-CT

Trial	n	PCa condition	Radiotherapy Dose	Follow-up (median)	Outcome	Results
SAKK 09/10 trial, 2021 [846]	350	pT2a-3b R0 – R1 pN0 or cN0 PSA post op undetectable (< 0.1 ng/mL) or persistent (> 0.1 ng/mL < 0.4 ng/mL)	64 Gy vs.70 Gy No ADT allowed VMAT+ IGRT: 57% 3-D planning: 43%	6.2 yr.	Primary endpoint: FFBP	**6 yr. FFBP:** **62% vs. 61%** **OS: no difference** **Late side effects:** **GI grade 2:** **7.3% vs. 20%** **GI grade 3:** **4.2% vs. 2.3%** p for ≥ grade 2/3: 0.009
Phase-III-Trial *Qi X, et al., 2020 [981]*	144 ART: 33% SRT: 67%	pT2-4 R0-R1 pN0 or cN0 Med. PSA pre-RT: 0.2 ng/mL	66 Gy vs. 72 Gy All patients VMAT+ IGRT No ADT allowed High risk (pT3-4, GS: 8-10, PSA>20 ng/mL): whole pelvis RT: 126 (87.5%)	49 mo.	Primary endpoint: FFBP	**4 yr. FFBP:** **75.9% vs. 82.6%** **(p > 0.05)** **High risk (GS: 8–10):** **55.7% vs. 79.7%** p < 0.049) **Late side effects:** **GI + GU grade 2** **p > 0.05** **No grade 3**

ADT = androgen deprivation therapy; ART = adjuvant radiotherapy; FFBP = freedom from biochemical failure; GI = gastro-intestinal; GU = genito-urinary; Gy = Gray; IGRT = image guided radiotherapy; mo = month; n = number of patients; PSA = prostate-specific antigen; RT = radiotherapy; SRT = y = year; vs. = versus; VMAT = volumetric arc radiation therapy.

Salvage RT is associated with toxicity. In one report on 464 SRT patients receiving median 66.6 (max. 72) Gy, acute grade 2 toxicity was recorded in 4.7% for both the GI and GU tract. Two men had late grade 3 reactions of the GI tract, but overall, severe GU tract toxicity was not observed. Late grade 2 complications occurred in 4.7% (GI tract) and 4.1% (GU tract), respectively, and 4.5% of the patients developed moderate urethral stricture [964].

In a RCT on dose escalation for SRT (n = 350), acute grade 2 and 3 GU toxicity was observed in 13.0% and 0.6%, respectively, with 64 Gy and in 16.6% and 1.7%, respectively, with 70 Gy. Gastro-intestinal tract grades 2 and 3 toxicity occurred in 16.0% and 0.6%, respectively, with 64 Gy, and in 15.4% and 2.3%, respectively, with 70 Gy [982, 983]. Late grade 2 and 3 GI toxicity was significantly increased with higher doses but without significant differences in QoL. In this study, however, the rectal wall dose constraints were rather permissive and in 44% of the patients outdated 3-D-techniques were used [980].

With dose escalation over 72 Gy and/or up to a median of 76 Gy, the rate of severe side effects, especially GU symptoms, clearly increases, even with newer planning and treatment techniques [984, 985]. In particular, when compared with 3D-CRT, IMRT was associated with a reduction in grade 2 GI toxicity from 10.2 to 1.9% (p = 0.02) but no effect on the relatively high level of GU toxicity was shown (5-year, 3D-CRT 15.8% vs. IMRT 16.8%) [984]. However, in a RCT comparing 66 Gy and 72 Gy with all patients having IMRT plus IGRT (n = 144), no significant differences for GI and GU-toxicity was demonstrated [981]. After a median salvage IMRT dose of 76 Gy however, the 5-year risk of grade 2–3 toxicity rose to 22% for GU and 8% for GI symptoms, respectively [985]. Doses of at least 64 Gy and up to 72 Gy in patients without PET/CT can be recommended [964, 982].

6.4.5.1.2.2 Salvage radiotherapy with or without ADT (cTx cN0/1) with PET/CT

In a prospective multi-centre study of 323 patients with BCR, PSMA PET/CT changed the management intent in 62% of patients as compared to conventional staging. This was due to a significant reduction in the number of men in whom the site of disease recurrence was unknown (77% vs. 19%, p < 0.001) and a significant increase in the number of men with metastatic disease (11% vs. 57%) [986].

A prospective study in a subgroup of 119 BCR patients with low PSA (< 0.5 ng/mL) reported a change in the intended treatment in 30.2% of patients [868]; however, no data exist on the impact on final outcome.

Another prospective study in 272 patients with early biochemical recurrent PCa after RP showed that ^{68}Ga-PSMA PET/CT may tailor further therapy decisions (e.g., local vs. systemic treatment) at low PSA values (0.2–1 ng/mL) [870].

A single-centre study retrospectively assessed 164 men who underwent imaging with PSMA PET/CT for a rising PSA after RP with PSA levels < 0.5 ng/mL. In men with a negative PSMA PET/CT who received SRT, 85% (23 out of 27) demonstrated a treatment response compared to a further PSA increase in 65% of those not treated (22 out of 34). In the 36/99 men with disease confined to the prostate fossa on PSMA, 83% (29 out of 36) responded to SRT [987]. Thus, PSMA PET/CT might stratify men into a group with high response (negative findings or recurrence confined to the prostate) and poor response (positive nodes or distant disease) to SRT.

A multi-centre retrospective study evaluated patients who underwent SRT for BCR after RP, without any signs of distant metastatic disease on PET/CT. After case-controle matching, two cohorts (n = 108 patients each), with and without PSMA PET/CT prior to SRT were analysed. In the cohort without PSMA PET/CT, 23 patients (21%) had BCR at one year after SRT vs. nine patients (8%) who underwent restaging with PSMA PET/C prior to SRT (p = 0.007). PSMA-PET/CT was found to be associated with an improved oncological outcome in patients with BCR after RP, receiving SRT to the prostatic fossa [988]. It is worth mentioning that in this study the median biologically effective radiation dose administered in the PSMA-cohort was significantly higher than in the historical cohort (70 Gy vs. 66 Gy, respectively, p < 0.001). However, in the SAKK 09/10 randomised phase-III-trial (all patients without PET-CT before SRT) the biochemical progression rate after SRT between patients who underwent 64 Gy or 70 Gy to the prostate bed, without HT for BCR, did not differ significantly [980]. Therefore, it is questionable whether this difference in administered radiation dose influenced the outcome in both cohorts. As there are no prospective phase III data including PET-CT before SRT (in particular not for PCa-specific survival or OS) these results have to be confirmed before a recommendation can be provided.

A single-centre open-label, phase II/III RCT (EMPIRE-1) evaluated the role of 18F-fluciclovine-PET/CT compared with conventional imaging for SRT. Three hundred and sixty five patients with detectable PSA after RP but negative results on conventional imaging, were randomised to RT directed by conventional imaging alone or to conventional imaging plus PET/CT; patients with M1 disease in the PET/CT group (n = 4) were excluded. Patients with cN1 were irradiated to the pelvic lymphatics but without a boost to the metastasis. Median follow 103 up was 3.5 years. In adjusted analyses, the study group was significantly associated with event-free survival (HR: 2.04, 95% CI: 1.06–3.93, p = 0.0327) [948].

6.4.5.1.2.3 Nodal-directed therapy for rcN1 (with PET/CT)

Radiolabelled PSMA PET/CT is increasingly used as a diagnostic tool to assess metastatic disease burden in patients with BCR following prior definitive therapy. A review including 30 studies and 4,476 patients showed overall estimates of positivity in a restaging setting of 38% in pelvic LNs and 13% in extra-pelvic LN metastases [867]. The percentage positivity of PSMA PET/CT was proven to increase with higher PSA values [867]. Results of this review demonstrated a high sensitivity and specificity of 68Ga-PSMA in advanced PCa, with a per-lesion-analysed sensitivity and specificity of 75% and 99%, respectively.

A large retrospective international study included patients with LN-recurrent PCa (cN1 and M1a) and PSA progression following multi-modality treatment (surgery and post-operative RT) [989]. The aim of the study was to compare standard of care (SOC) with nodal metastasis-directed therapy (MDT). The nodal MDT-group showed significantly better CSS than the SOC control group (5-year survival 98.6% vs. 95.7%, p < 0.01, respectively) [989].

Another retrospective study compared SBRT with elective nodal irradiation (ENRT) in nodal oligo-recurrent PCa (n = 506 patients, 365 of which with N1 pelvic recurrence). With a median follow-up of 36 months, ENRT (n = 197) was associated with a significant reduction of nodal recurrences (p < 0.001), compared with SABR (n = 309) of 2% vs. 18%, respectively. In multi-variable analysis, patients with one LN at recurrence had longer adjusted MFS after ENRT (HR: 0.50, 95% CI: 0.30–0.85, p = 0.009). The tendency to relapse was higher for pelvic- than extra-pelvic nodes (p < 0.001) [990]. For patients presenting with two or more (extra)pelvic LNs, adjusted MFS was not significantly different (HR: 0.92, 95% CI: 0.54– 1.59, p = 0.8). In these situations, SABR should be used in highly selected patients in prospective cohorts or clinical trials only, before any recommendations can be made. For MDT in M1 patients see Section 6.4.7.

6.4.5.1.3 Salvage lymph node dissection

The surgical management of recurrent nodal metastases in the pelvis has been the topic of several retrospective analyses [991-993] and a SR [994]. The reported five-year BCR-free survival rates ranged from 6% to 31%. Five-year OS was approximately 84% [994]. Biochemical recurrence rates were found to be dependent on PSA at salvage surgery and location and number of positive nodes [995]. Addition of RT to the lymphatic template after salvage LN dissection may improve the BCR rate [996]. In a multi-centre retrospective study long-term outcomes of 189 patients who underwent salvage LN dissection were reported to be worse than previously described in studies with shorter follow-up [997]. Biochemical recurrence (BCR)-free survival at ten years was 11%. Patients with a PSA response after salvage LN dissection and patients receiving ADT within six months from salvage LN dissection had a lower risk of death from PCa [997]. The majority of the patients (81%) had received a choline PET and median PSA at salvage LN dissection was 2.5 ng/mL. In a cohort study including patients treated with salvage LN dissection via PSMA–radioguided surgery (PSMA-RGS), two-year BCR-free survival rate was 32% [998]. In multi-variable analyses, higher pre-operative PSA, higher number of PSMA-avid lesions, multiple (pelvic plus retroperitoneal), and retroperitoneal localisation of lesions at pre-operative imaging were independent predictors of BCR after PSMA-RGS. High-level evidence for the oncological value of salvage LN dissection (including adjuvant RT of the LNs) is still lacking [994].

6.4.5.2 Management of PSA failures after radiation therapy

Therapeutic options in these patients are ADT or salvage local procedures, as well as a 'wait and see' approach, based on EAU BCR risk categories at relapse. A SR and meta-analysis included studies comparing the efficacy and toxicity of salvage RP, salvage HIFU, salvage cryotherapy, SBRT, salvage LDR BT, and salvage HDR BT in the management of locally recurrent PCa after primary radical EBRT [999]. The outcomes were BCR-free survival at two and five years. No significant differences with regards to recurrence-free survival (RFS) between these modalities was found. Five-year RFS ranged from 50% after cryotherapy to 60% after HDR BT and SBRT. The authors reported that severe GU toxicity exceeded 21% for HIFU and RP, whereas it ranged from 4.2% to 8.1% with re-irradiation. Differences in severe GI toxicity also appeared to favour re-irradiation, particularly HDR BT [999]. Due to the methodological limitations of this review (the majority of the included studies were uncontrolled single-arm case series and there was considerable heterogeneity in the definitions of core outcomes) the available evidence for these treatment options is of low quality and strong recommendations regarding the choice of any of these techniques cannot be made. The following is an overview of the most important findings for each of these techniques.

6.4.5.2.1 Salvage radical prostatectomy

Salvage RP after RT is associated with a higher likelihood of AEs compared to primary surgery because of the risk of fibrosis and poor wound healing due to radiation [1000].

6.4.5.2.1.1 Oncological outcomes

In a SR of the literature, Chade, *et al.*, showed that SRP provided five and ten years BCR-free survival estimates ranging from 47–82% and from 28–53%, respectively. The ten-year CSS and OS rates ranged from 70–83% and from 54–89%, respectively. The pre-SRP PSA value and prostate biopsy ISUP grade group were the strongest predictors of the presence of organ-confined disease, progression, and CSS [1001]. In a multi-centre analysis including 414 patients, five-year BCR-free survival, CSS and OS were 56.7%, 97.7% and 92.1%, respectively [1002]. Pathological T stage ≥ T3b (OR: 2.348) and GS (up to OR 7.183 for GS > 8) were independent predictors for BCR (see Table 6.4.7).

Table 6.4.7: Oncological results of selected salvage radical prostatectomy case series

Study	n	Median FU (mo)	Pathologic Organ-confined (%)	PSM (%)	Lymph-node involvement (%)	BCR-free probability (%)	CSS (%)	Time probability
Chade, *et al.* 2011 [1003]	404	55	55	25	16	37	83	10 yr.
Mandel, *et al.* 2016 [1004]	55	36	50	27	22	49	89	5 yr.
Ogaya-Pinies, *et al.* 2018 [1005]	96	14	50	17	8	85*	-	14 mo.
Marra, *et al.* 2021 [1002]	414	36	46	30	16	57	98	5 yr.

**Percentage of patients without BCR.*

BCR = biochemical recurrence; CSS = cancer-specific survival; FU = follow-up; mo = months; n = number of patients; PSM = positive surgical margin; yr. = year.

6.4.5.2.1.2 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%) [1006]. A series, these complications appear to be less common [1000, 1001, 1004].

Functional outcomes are also worse compared to primary surgery, with urinary incontinence ranging from 21% to 90% and ED in nearly all patients [1001, 1004].

6.4.5.2.1.3 Summary of salvage radical prostatectomy

In general, SRP should be considered only in patients with low co-morbidity, a life expectancy of at least ten years, a pre-SRP PSA < 10 ng/mL and initial biopsy ISUP grade group ≤ 2/3, no LN involvement or evidence of distant metastatic disease pre-SRP, and those whose initial clinical staging was T1 or T2 [1001].

6.4.5.2.2 Salvage cryoablation of the prostate

6.4.5.2.2.1 Oncological outcomes

Salvage cryoablation of the prostate (SCAP) has been proposed as an alternative to salvage RP, as it has a potentially lower risk of morbidity and equal efficacy.

In a SR a total of 32 studies assessed SCAP, recruiting a total of 5,513 patients. The overwhelming majority of patients (93%) received whole-gland SCAP. The adjusted pooled analysis for two-year BCR-free survival for SCAP was 67.49% (95% CI: 61.68–72.81%), and for five-year BCR-free survival was 50.25% (95% CI: 44.10–56.40%). However, the certainty of the evidence was low. Table 6.3.8 summarises the results of a selection of the largest series on SCAP to date in relation to oncological outcomes (BCR only) [999] (Table 6.4.8).

Table 6.4.8: Oncological results of selected salvage cryoablation of the prostate case series, including at least 250 patients

Study	n	Median FU (mo)	Time point of outcome measurement (yr)	BCR-free probability	Definition of failure
Ginsburg, *et al.* 2017 [1007]	898	19.0	5	71.3%	Phoenix criteria
Spiess, *et al.* 2010 [1008]	450	40.8	3.4	39.6%	PSA > 0.5 ng/mL
Li, *et al.* 2015 [1009]	486	18.2	5	63.8%	Phoenix criteria
Kovac, *et al.* 2016 [1010]	486	18.2	5	75.5% (nadir PSA < 0.4 ng/mL); 22.1% (nadir PSA ≥ 0.4 ng/mL)	Phoenix criteria
Ahmad, *et al.* 2013 [1011]	283	23.9	3	67.0% (nadir PSA ≤ 1 ng/mL); 14.0% (nadir PSA > 1 ng/mL)	Phoenix criteria
Pisters, *et al.* 2008 [1012]	279	21.6	5	58.9% (ASTRO) 54.5% (Phoenix)	ASTRO and Phoenix criteria

ASTRO = American Society for Therapeutic Radiology and Oncology; BCR = biochemical recurrence; FU = follow-up; mo. = months; n = number of patients; PSA = prostate-specific antigen; yr. = year.

6.4.5.2.3 Salvage re-irradiation

6.4.5.2.3.1 Salvage brachytherapy for radiotherapy failure

Carefully selected patients with a good PS, primary localised PCa, good urinary function and histologically proven local recurrence are candidates for salvage BT using either HDR or LDR.

In a SR a total of sixteen studies (four prospective) and 32 studies (two prospective) assessed salvage HDR and LDR BT, respectively, with the majority (> 85%) receiving whole-gland BT rather than focal treatment [999]. The adjusted pooled analysis for two-year BCR-free survival for HDR was 77% (95% CI: 70–83%) and for LDR was 81% (95% CI:74–86%). The five-year BCR-free survival for HDR was 60% (95% CI: 52–67%) and for LDR was 56% (95% CI: 48–63%). As noted above, BT techniques are associated with lower rates of severe GU toxicity when compared to RP or HIFU, at 8% for HDR (95% CI: 5.1–11%) and 8.1% for LDR (95% CI: 4.3–13%). Rates of severe GI toxicity are reported to be very low at 0% for HDR (95% CI: 0–0.2%) and 1.5% for LDR (95% CI: 0.2–3.4%). High-dose-rate or LDR BT are effective treatment options with an acceptable toxicity profile. However, the published series are small and likely under-report toxicity. Consequently, this treatment should be offered in experienced centres ideally within randomised clinical trials or prospective registry studies (see Table 6.4.9).

Table 6.4.9: Treatment-related toxicity and BCR-free probability in selected salvage brachytherapy studies including at least 100 patients.

Study	Study design	n and BT type	Median FU (mo)	Treatment toxicity	BCR-free probability
Lopez, *et al.* 2019 [1013]	multi-centre retrospective	75 HDR 44 LDR	52	23.5% late G3+ GU	5 yr 71% (95% CI: 65.9-75.9%)
Crook, *et al.* 2019 [1014]	multi-centre prospective	100 LDR	54	14% late G3 combined GI/GU	n.r.
Smith, *et al.* 2020 [1015]	single-centre retrospective	108 LDR	76	15.7%/2.8% late G3 GU/GI	5 yr. 63.1% 10 yr. 52%
Lyczek, *et al.* 2009 [1016]	single-centre retrospective	115 HDR	n.r.	12.2%/0.9% late G3+ GU/GI	60% at 40 mo.

BT = brachytherapy; CI = confidence interval; G = grade; GI = gastro-intestinal; GU = genito-urinary; HDR = high-dose rate; LDR = low-dose rate; mo = months; n = number of patients; n.r. = not reported; yr = year.

6.4.5.2.3.2 Salvage stereotactic ablative body radiotherapy for radiotherapy failure

6.4.5.2.3.2.1 Oncological outcomes and morbidity

Stereotactic ablative body radiotherapy (CyberKnife® or linac-based treatment) is a potentially viable new option to treat local recurrence after RT. Carefully selected patients with good IPSS-score, without obstruction, good PS and histologically proven localised local recurrence are potential candidates for SABR. In a metaanalysis and SR five mostly retrospective studies including 206 patients were treated with CyberKnife® or linac-based treatment showing two-year RFS estimates (61.6%, 95% CI: 52.6–69.9%) [999]. In a retrospective multi-centre study (n = 100) the median pre-salvage PSA was 4.3 ng/mL with 34% of patients having received ADT for twelve months (median). All recurrences were biopsy proven. Patients were treated with the CyberKnife® with a single dose of 6 Gy in six daily fractions (total dose 36 Gy). With a median followup of 30 months the estimated three-year second BCR-free survival was 55% [1017].

In a smaller retrospective series including 50 men with histologically proven local recurrence with a median pre-salvage PSA of 3.9 ng/mL only 15% had received additional ADT. The estimated five-year second BCR-free survival was 60% (median follow-up of 44 months) which is an outcome comparable to series treating patients with RP, HIFU or BT [1018]. Table 6.4.10 summarises the results of the two larger SABR series addressing oncological outcomes and morbidity.

Table 6.4.10: Treatment-related toxicity and BCR-free survival in selected SABR studies

Study	Study design	n and RT-type	Median FU (mo)	Fractionation (SD/TD)	ADT	Treatment toxicity	BCR-free survival
Bergamin, *et al.* 2020 [1019]	single-centre prospective	25 LINAC based	25	SD 6-6.2 TD 36-38 Gy	0/25	2 yr. late G1 GI 8% G2 GU 4%	2 yr. 80%
Fuller, *et al.* 2020 [1018]	single-centre retrospective	50 Cyber Knife	44	SD 6.8 Gy TD 34 Gy	7/50	5 yr: 8% late G3+ GU	5 yr. 60%
Pasquier, *et al.* 2020 [1017]	multi-centre retrospective	100 Cyber Knife	30	SD 6 Gy TD 36 Gy	34/100 median 12 mo.	3 yr. grade 2+ GU 20.8% GI 1%	3 yr. 55%

BCR = biochemical recurrence; FU = follow-up; mo = months; n = number of patients; RT-type = type of radio-therapy; SD = single dose; TD = total dose; yr = year.

6.4.5.2.3.2.2 Morbidity

In a retrospective single-centre study with 50 consecutive patients chronic significant toxicity was only seen for the GU domain with five-year grade 2+ and grade 3+ GU rates of 17% and 8%, respectively. No GI toxicity > grade 1 was seen. Of note, of the fifteen patients who were sexually potent pre-salvage SBRT, twelve subsequently lost potency [1018]. In a retrospective French (GETUG) multi-centre series (n = 100) the three-year late grade 2+ GU and GI toxicity was 20.8% (95% CI: 13–29%) and 1% (95% CI: 0.1–5.1%), respectively [1017].

6.4.5.2.3.2.3 Summary of salvage stereotactic ablative body radiotherapy

Despite the encouraging results so far the number of patients treated with SABR is relatively limited. In view of the rates of higher grade 2+ GU side effects, SABR should only be offered to selected patients, in experienced centres as part of a clinical trial or well-designed prospective study.

6.4.5.2.4 Salvage high-intensity focused ultrasound

6.4.5.2.4.1 Oncological outcomes

Salvage HIFU has emerged as an alternative thermal ablation option for radiation-recurrent PCa. Being relatively newer than SCAP the data for salvage HIFU are even more limited. A SR and metaanalysis included 20 studies (n = 1,783) assessing salvage HIFU [999]. The overwhelming majority of patients (86%) received whole-gland salvage HIFU. The adjusted pooled analysis for two-year BCR-free survival for salvage HIFU was 54.14% (95% CI: 47.77–60.38%) and for five-year BCR-free survival 52.72% (95% CI: 42.66– 62.56%). However, the certainty of the evidence was low. Table 6.4.11 summarises the results of a selection of the largest series on salvage HIFU to date in relation to oncological outcomes (BCR only).

Table 6.4.11: Oncological results of selected salvage cryoablation of the prostate case series, including at least 250 patients

Study	n	Median FU (mo)	Time point of outcome measurement (yr)	BCR-free probability	Definition of failure
Crouzet, *et al.* 2017 [1020]	418	39.6	5	49.0%	Phoenix criteria
Murat, *et al.* 2009 [1021]	167	Mean 18.1	3	25.0% (high-risk) 53.0% (low-risk)*	Phoenix criteria or positive biopsy or initiation of post-HIFU salvage therapy
Kanthabalan, *et al.* 2017 [1022]	150	35.0	3	48.0%	Phoenix criteria
Jones, *et al.* 2018 [1023]	100	12.0	1	50.0%	Nadir PSA > 0.5 ng/mL or positive biopsy

**Results stratified by pre-EBRT D'Amico risk groups.*

BCR = biochemical recurrence; FU = follow-up; mo = months; n = number of patients; yr = year.

6.4.5.2.4.2 Morbidity

The main adverse effects and complications relating to salvage HIFU include urinary incontinence, urinary retention due to bladder outflow obstruction, rectourethral fistula and ED. The SR and meta-analysis showed an adjusted pooled analysis for severe GU toxicity for salvage HIFU of 22.66% (95% CI: 16.98–28.85%) [999]. The certainty of the evidence was low. Table 6.4.12 summarises the results of a selection of the largest series on salvage HIFU to date in relation to GU outcomes.

Table 6.4.12: Peri-operative morbidity, erectile function and urinary incontinence in selected salvage HIFU case series, including at least 100 patients

Study	n	Time point of outcome measurement (yr)	Incontinence* (%)	Obstruction/ retention (%)	Rectourethral fistula (%)	ED (%)
Crouzet, *et al.* 2017 [1020]	418	Median 39.6	42.3	18.0	2.3	n.r.
Murat, *et al.* 2009 [1021]	167	Median 18.1	49.5	7.8	3.0	n.r.
Kanthabalan, *et al.* 2017 [1022]	150	24	12.5	8.0	2.0	41.7
Jones, *et al.* 2018 [1023]	100	12	42.0	49.0	5.0	74.0

**Incontinence was heterogeneously defined; figures represent at least 1 pad usage.*

ED = erectile dysfunction; n.r. = not reported; n = number of patients.

6.4.5.2.4.3 Summary of salvage high-intensity focused ultrasound

There is a lack of high-certainty data which prohibits any recommendations regarding the indications for salvage HIFU in routine clinical practice. There is also a risk of significant morbidity associated with its use in the salvage setting. Consequently, salvage HIFU should only be performed in selected patients in experienced centres as part of a clinical trial or well-designed prospective cohort study.

*6.4.6 **Hormonal therapy for relapsing patients***

The Panel conducted a SR including studies published from 2000 onwards [1024]. Conflicting results were found on the clinical effectiveness of HT after previous curative therapy of the primary tumour. Some studies reported a favourable effect of HT, including the only RCT addressing the research question of this review (86% vs. 79% advantage in OS in the early HT group) [1025]. Other studies did not find any differences between early vs. delayed, or no, HT. One study found an unfavourable effect of HT [1026]. This may be the result of selecting clinically unfavourable cases for (early) HT and more intensive diagnostic workup and follow-up in these patients.

The studied population is highly heterogeneous regarding their tumour biology and therefore clinical course. Predictive factors for poor outcomes were short PSA-DT, high ISUP grade group, high PSA, increased age and comorbidities. In some studies, such as the Boorjian, *et al.*, study [1027], high-risk patients, mainly defined by a high ISUP grade group and a short PSA-DT (most often less than six months) seem to benefit most from (early) HT, especially men with a long life expectancy.

Non-steroidal anti-androgens have been claimed to be inferior compared to castration, but this difference was not seen in M0 patients [960]. One of the included RCTs suggested that intermittent HT is not inferior to continuous HT in terms of OS and CSS [1028]. A small advantage was found in some QoL domains but not overall QoL outcomes. An important limitation of this RCT is the lack of any stratifying criteria such as PSA-DT or initial risk factors. Based on the lack of definitive efficacy and the undoubtedly associated significant side effects, patients with recurrence after primary curative therapy should not receive standard HT since only a minority of them will progress to metastases or PCa-related death. The objective of HT should be to improve OS, postpone distant metastases, 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 [1029, 1030]. Early HT should be reserved for those at the highest risk of disease progression defined mainly by a short PSA-DT at relapse (< 6–12 months) or a high initial ISUP grade group (> 2/3) and a long life expectancy.

A three-arm randomised phase III trial (EMBARK) looked at patients with prostate cancer who had high-risk biochemical recurrence defined as a PSA-DT of ≤9 months and a PSA level of ≥2 ng/ml above the nadir after radiation therapy or ≥1 ng/ml after radical prostatectomy with or without postoperative radiation therapy [1031]. Patients were randomly assigned 1:1:1 to receive enzalutamide daily plus leuprolide every 12 weeks (combination group), placebo plus leuprolide (leuprolide-alone group), or enzalutamide monotherapy (monotherapy group). The primary end point was MFS, in the combination group as compared with the leuprolide- alone group. The MFS in the monotherapy group as compared with the leuprolide-alone group was a key secondary endpoint. A total of 1068 patients were randomised. After a median follow-up of 60.7 months, the five year - MFS was 87.3% (95% CI, 83.0 - 90.6) in the combination group, 71.4% (95% CI, 65.7 - 76.3) in the leuprolide-alone group, and 80.0% (95% CI, 75.0 - 84.1) in the monotherapy group. The combination of enzalutamide plus leuprolide was superior to leuprolide alone with regards to the MFS (HR 0.42; 95% CI, 0.30 - 0.61; P<0.001). Enzalutamide monotherapy also showed a superior MFS compared to leuprolide alone (HR 0.63; 95% CI, 0.46 - 0.87; P = 0.005). These results led to the FDA approval for enzalutamide alone or in combination with ADT for patients with high-risk biochemical recurrence in November 2023 [1032].

At the time of the MFS analysis, OS data were immature with 12% deaths in the overall population. Also, an intermittent treatment approach can be considered. Enzalutamide treatment can be suspended if PSA is undetectable (< 0.2 ng/mL) after 36 weeks of therapy. Treatment may be reinitiated when PSA has increased to ≥ 2.0 ng/mL for patients who had prior radical prostatectomy or ≥ 5.0 ng/mL for patients who had prior primary radiation therapy. There were no new safety signals. Of note, at a median follow-up of five years, the overall percentage of patients who had fractures was 14% [1033].

6.4.7 *Observation*

In unselected relapsing 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 five years [825]. For patients with EAU Low-Risk BCR features (see Section 6.3.3), unfit patients with a life expectancy of less than ten years or patients unwilling to undergo salvage treatment, active follow-up may represent a viable option.

6.4.8 *Guidelines for second-line therapy after treatment with curative intent*

Local salvage treatment	Strength rating
Recommendations for biochemical recurrence (BCR) after radical prostatectomy	
Offer early salvage intensity-modulated radiotherapy/volumetric arc radiation therapy plus image-guided radiotherapy to men with two consecutive PSA rises.	Strong
A negative positron emission tomography/computed tomography (PET/CT) scan should not delay salvage radiotherapy (SRT), if otherwise indicated.	Strong
Offer monitoring, including prostate-specific antigen (PSA), to EAU Low-Risk BCR patients.	Weak
Do not wait for a PSA threshold before starting treatment. Once the decision for SRT has been made, SRT (at least 64 Gy) should be given as soon as possible.	Strong
Offer hormonal therapy in addition to SRT to men with BCR.	Weak
Recommendations for BCR after radiotherapy	
Offer monitoring, including PSA to EAU Low-Risk BCR patients.	Weak
Only offer salvage radical prostatectomy (RP), brachytherapy, stereotactic body radiotherapy, high-intensity focused ultrasound, or cryosurgical ablation to highly selected patients with biopsy-proven local recurrence within a clinical trial setting or well-designed prospective cohort study undertaken in experienced centres.	Strong
Recommendations for systemic salvage treatment	
Do not offer androgen deprivation therapy to M0 patients with a PSA-doubling time > twelve months.	Strong
Offer enzalutamide with or without androgen deprivation therapy to M0 patients with high-risk BCR, defined as a PSA doubling time of ≤9 months and a PSA level of ≥2ng/ml above nadir after radiation therapy or ≥1 ng/ml after radical prostatectomy with or without postoperative radiation therapy.	Strong
Recommendations for follow-up after radical prostatectomy or radiotherapy	
Routinely follow-up asymptomatic patients by obtaining at least a disease-specific history and serum prostate-specific antigen (PSA) measurement.	Strong
At recurrence, only perform imaging if the result will affect treatment planning.	Strong

6.5 Systemic treatments for prostate cancer

6.5.1 *Hormonal therapy*

6.5.1.1 *Different types of hormonal therapy*

Androgen deprivation can be achieved by suppressing the secretion of testicular androgens in different ways. This can be combined with inhibiting the action of circulating androgens at the level of their receptor which has been known as complete (or maximal or total) androgen blockade (CAB) using the old-fashioned antiandrogens [1034].

6.5.1.2 *Castration level*

The castration level of testosterone is < 50 ng/dL (1.7 nmol/L), which was defined more than 40 years ago when testosterone testing was less sensitive. Current methods have shown that the mean value after surgical castration is 15 ng/dL [1035]. Therefore, a more appropriate level should be defined as < 20 ng/dL (< 0.7 nmol/L). This definition is important as better results are repeatedly observed with lower testosterone levels compared to 50 ng/dL [1036-1038]. However, the castrate level considered by the regulatory authorities and in clinical trials addressing castration in PCa is still the historical < 50 ng/dL (1.7 nmol/L).

6.5.1.3 *Bilateral orchiectomy*

Bilateral orchiectomy or subcapsular pulpectomy is still considered the primary treatment modality for ADT. It is a simple, cheap and virtually complication-free surgical procedure. It is easily performed under local anaesthesia, and it is the quickest way to achieve a castration level which is usually reached within less than twelve hours. It is irreversible and therefore does not allow for intermittent treatment [1039].

6.5.1.4 Oestrogens

Treatment with oestrogens results in testosterone suppression and is not associated with bone loss [1040]. Early studies tested oral diethylstilboestrol (DES) at several doses. Due to severe side effects, especially thromboembolic complications, even at lower doses these drugs are not considered as standard first-line treatment [1041, 1042]. Oestrogen patches are under investigation [1043].

6.5.1.5 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. The first injection induces a transient rise in luteinising hormone (LH) and follicle-stimulating hormone (FSH) leading to the 'testosterone surge' or 'flare-up' phenomenon which starts two to three days after administration and lasts for about one week. This may 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 [1044]. 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. Anti-androgen therapy is usually continued for four weeks but neither the timing nor the duration of anti-androgen therapy are based on strong evidence. In addition, the long-term impact of preventing 'flare up' is unknown [1045].

Chronic exposure to LHRH agonists results in the down-regulation of LHRH-receptors, suppressing LH and FSH secretion and therefore testosterone production. A castration level is usually obtained within two to four weeks [1046]. Although there is no formal direct comparison between the various compounds, they are considered to be equally effective [1047]. So far, no survival difference between LHRH agonists and orchiectomy has been reported due to the lack of high-quality trials [1048].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.

6.5.1.6 Luteinising-hormone-releasing hormone antagonists

Luteinising-hormone-releasing hormone antagonists immediately bind to LHRH receptors, leading to a rapid decrease in LH, FSH and testosterone levels without any flare. The practical shortcoming of these compounds is the lack of a long-acting depot formulation with, so far, only monthly formulations being available. Degarelix is a LHRH antagonist. The standard dosage is 240 mg in the first month followed by monthly injections of 80 mg. Most patients achieve a castrate level at day three [1046]. A phase III RCT compared degarelix to monthly leuprorelin following up patients for twelve months, suggesting a better PSA PFS for degarelix 240/80 mg compared to monthly leuprorelin [1049]. A SR did not show a major difference between agonists and degarelix and highlighted the paucity of on-treatment data beyond twelve months as well as the lack of survival data [1050]. Its definitive superiority over the LHRH analogues remains to be proven. Short-term follow-up data from a meta-analysis indicate that the use of LHRH antagonist is associated with significantly lower overall mortality and cardiovascular events as compared with agonists. On the other hand, other adverse effects such as decreased libido, hot flushes, ED, weight gain, and injection site reactions are seen less often with the agonists [1051, 1052].

Relugolix is an oral LHRH antagonist. It was compared to the LHRH agonist leuprolide in a randomised phase III trial [1053]. The primary endpoint was sustained testosterone suppression to castrate levels through 48 weeks. There was a significant difference of 7.9 percentage points (95% CI: 4.1–11.8) showing non-inferiority and superiority of relugolix. The incidence of major adverse cardiovascular events was significantly lower with relugolix (prespecified safety analysis). Relugolix has been approved by the FDA [1054] and EMA [1055] for hormone sensitive PCa.

6.5.1.7 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 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.

6.5.1.7.1 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.

Cyproterone acetate was the first licensed anti-androgen but the least studied. Its most effective dose as monotherapy is still unknown. Although CPA has a relatively long half-life (31–41 hours), it is usually administered in two or three fractionated doses of 100 mg each. In one RCT CPA showed a poorer OS when compared with LHRH analogues [1056]. An underpowered RCT comparing CPA monotherapy with flutamide in M1b PCa did not show any difference in DSS and OS at a median follow-up of 8.6 years [1057]. Other CPA monotherapy studies suffer from methodological limitations preventing firm conclusions.

6.5.1.7.2 Non-steroidal anti-androgens

Non-steroidal anti-androgen monotherapy with e.g. nilutamide, flutamide or bicalutamide does not suppress testosterone secretion and it is claimed that libido, overall physical performance and bone mineral density (BMD) are frequently preserved [1058]. Non-androgen-related pharmacological side effects differ between agents. Bicalutamide shows a more favourable safety and tolerability profile than flutamide and nilutamide [1059]. The dosage licensed for use in CAB is 50 mg/day, and 150 mg/day for monotherapy. The androgen pharmacological side effects are mainly gynaecomastia (70%) and breast pain (68%). However, non-steroidal anti-androgen monotherapy offers clear bone protection compared with LHRH analogues and probably LHRH antagonists [1058, 1060]. All three agents share the potential for liver toxicity (occasionally fatal), requiring regular monitoring of patients' liver enzymes.

6.5.1.7.3 New androgen receptor pathway inhibitors (ARPis)

Once on ADT the development of castration-resistance (CRPC) is only a matter of time. It is considered to be mediated through two main overlapping mechanisms: androgen-receptor (AR)-independent and AR-dependent mechanisms (see Section 6.5 - Castrate-resistant PCa). In CRPC, the intracellular androgen level is increased compared to androgen sensitive cells and an over-expression of the AR has been observed, suggesting an adaptive mechanism [1061]. This has led to the development of several new compounds targeting the androgen axis. In mCRPC, abiraterone acetate and enzalutamide have been approved. In addition to ADT (sustained castration), abiraterone acetate, apalutamide and enzalutamide have been approved for the treatment of metastatic hormone sensitive PCa (mHSPC) by the FDA and the EMA. For the updated approval status see EMA and FDA websites [1032, 1062-1065]. Finally, apalutamide, darolutamide and enzalutamide have been approved for non-metastatic CRPC (nmCRPC) at high risk of further metastases [1066-1070].

6.5.1.7.3.1 Abiraterone acetate

Abiraterone acetate is a CYP17 inhibitor (a combination of 17α-hydrolase and 17,20-lyase inhibition). By blocking CYP17, abiraterone acetate 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 to prevent drug-induced hyperaldosteronism [1062, 1064].

6.5.1.7.3.2 Apalutamide, darolutamide, enzalutamide (alphabetical order)

These agents are novel non-steroidal anti-androgens with a higher affinity for the AR receptor than traditional non-steroidal anti-androgens. In addition, while previous non-steroidal anti-androgens still allow transfer of ARs to the nucleus and would act as partial agonists, all three agents also block AR transfer and therefore suppress any possible agonist-like activity [1065-1067]. Darolutamide has structurally unique properties In particular, in preclinical studies, it was shown not to cross the blood-brain barrier [1071, 1072].

*6.5.2 **Cytotoxic drug treatment***

6.5.2.1 Taxanes

Paclitaxel derivatives promote the assembly of microtubules and inhibit the subsequent depolymeization, impairing the tubulin dynamics that foster the mitotic spindle assembly during interphase in mitosis [1073]. Docetaxel binds ß-tubulin dimers in a 1:1 stoichiometric ratio, exhibiting a stronger dynamic instability using its inhibitory effect in tubulin depolymerization [1074]. It also activates NF-kB causing apoptosis via a mitochondria-dependent pathway [1075]. Docetaxel shows significant activity against prostatetumours. Cabazitaxel also works by binding to the microtubules. This prevents cellular mitosis and stabilises the tumour cells. As a result, the cells do not divide. In addition, it inhibits androgen receptors by binding to the microtubules and microtubule-associated motor protein dynein. As a consequence, androgen receptor nuclear translocation is prevented [1073]. Common side-effects include peripheral neuropathy, myalgias, neutropenia and arthralgia.

*6.5.3 **Non-hormonal non-cytotoxic drug treatments***

6.5.3.1 Poly (ADP-ribose) polymerase inhibitirs (PARPi)

Poly (ADP-ribose) polymerase inhibitors (PARPi) block the enzyme poly ADP-ribose polymerase (PARP) and were developed aiming to selectively target cancer cells harbouring BRCA mutations and other mutations inducing homologous recombination deficiency and high level of replication pressure with a sensitivity to PARPi treatment. Due to the oncogenic loss of some DNA repair effectors and incomplete DNA repair repertoire, some cancer cells are addicted to certain DNA repair pathways such as Poly (ADP-ribose) polymerase (PARP)-related single-strand break repair pathway. The interaction between BRCA and PARP is a form of synthetic lethal effect which means the simultaneously functional loss of two genes leads to cell death, while a defect in any single gene only has a limited effect on cell viability [1076]. The therapeutic indications for PCa are discussed in Sections 6.5.8.1.

6.5.3.2 AKT inhibitors

AKT inhibitors are small molecules which are designed to target and bind to all three isoforms of AKT, which is a key component of the PI3K/AKT pathway. In clinical trials, ipatasertib, an oral, highly specific, AKT inhibitor was used and showed significant activity when combined with abiraterone acetate in patients with loss of the tumour suppressor protein PTEN on immunohistochemistry within the tumour [1077, 1078]. Available data can be found in table 6.5.2. Currently, there are no approved AKT inhibitors.

6.5.3.3 Immune checkpoint inhibitors

Checkpoint inhibitors target the molecules CTLA4, programmed cell death protein 1 (PD-1), and programmed death-ligand 1 (PD-L1). For advanced PCa patients that are microsatellite instability-high/deficient mismatch repair (MSI-H/*dMMR*), the PD-1 inhibitor pembrolizumab has been approved by the FDA but not by the EMA. The label is tumour agnostic [1079, 1080]. See also Section 6.6.2.1

6.5.3.4 Radiopharmaceutical therapy

Radiopharmaceutical therapy (RPT) is based on the delivery of radioactive isotopes to tumour-associated targets. The mechanism of action for RPT is radiation-induced killing of cells. Radionuclides with different emission properties are used to deliver radiation. The most commonly used radionuclides are represented by β-particles (e.g., ^{177}Lu) or α-particles (e.g., ^{223}Ra, ^{225}Ac). ^{177}Lu is increasingly used because of its optimal imaging range (100–200 keV), favourable half time (6.6 days) and appropriate β-particle energy for therapy. The short path of the β-particles (0.05–0.08 mm) results in minimal toxic effects in adjacent healthy tissue. These properties enable such radionuclides to be used as theranostics (i.e., the same radionuclide may be used for both diagnostic and therapeutic purposes). However, an essential requirement prior to any RPT is to assess the targeting of the agent, mainly using PET techniques which show the tumour expression and the extent of cancer [1081]. ^{177}Lu has been approved by the FDA for the treatment of adult patients with PSMA-positive mCRPC who have been treated with ARPI and taxane-based chemotherapy [1082, 1083]. Clinical details are discussed in Section 6.6.8.

6.6 Management of Metastatic prostate cancer

*6.6.1 **Introduction***

All prospective data available rely on the definition of M1 disease based on CT scan or MRI and bone scintigraphy. The influence on treatment and outcome of newer, more accurate, imaging has not been assessed yet.

*6.6.2 **Prognostic factors***

Median survival of patients with newly diagnosed metastases (synchronous mHSPC) is approximately 50 months with ADT alone, however, it is highly variable since the M1 population is heterogeneous [1084]. Several prognostic factors for survival have been suggested including the number and location of bone metastases, presence of visceral metastases, ISUP grade group, PS status and initial PSA and alkaline phosphatase level, but only few have been validated [1085-1088].

'Volume' of disease as a potential predictor was introduced by CHAARTED (Chemo-hormonal Therapy versus Androgen Ablation Randomised Trial for Extensive Disease in Prostate Cancer) [1088-1090] (see table 6.4.1) and subsequently, in STAMPEDE, was shown to be predictive in an adequately powered subgroup analysis for benefit of addition of prostate RT to ADT in the subgroup of patients with low volume/burden disease [1091] (See table 6.4.1).

'Metachronous' metastatic disease (after radical local treament of the primary tumour) vs. synchronous (or *de novo*) metastatic disease has also been shown to have generally a better prognosis [1092].

Based on a large SWOG 9346 cohort, the PSA level after seven months of ADT was used to create three prognostic groups (see Table 6.4.2) [1093]. A PSA ≤ 0.2 ng/mL at seven months has been confirmed as

a prognostic marker for men receiving ADT for metastatic disease in the CHAARTED study independent of the addition of docetaxel [1094]. Similarly reaching PSA levels of ≤ 0.1ng/ml after six months were shown to be correlated with long-term outcomes in the LATITUDE study [1095]. Also for patients treated with ADT and apalutamide a deep PSA decline defined by ≥ 90% from baseline or to PSA≤ 0.2 ng/ml at a landmark of three months was associated with longer OS [1096] for patients.

Table 6.6.2.1 Definition of high- and low-volume in CHAARTED [1088-1090] and high- and low-risk in LATITUDE [1070]

	High	Low
CHAARTED (volume)	≥ 4 Bone metastases including ≥ 1 outside vertebral column or pelvis **AND/OR** Visceral metastasis*	Not high
LATITUDE (risk)	≥ 2 high-risk features of: • ≥ 3 Bone metastasis • Visceral metastasis • ≥ ISUP grade 4	Not high

**Lymph nodes are not considered as visceral metastases.*

Table 6.6.2.2: Prognostic factors based on the SWOG 9346 study [1093]

PSA after 7 months after start of ADT	Median survival on ADT monotherapy
< 0.2 ng/mL	75 months
0.2 ≤ 4 ng/mL	44 months
> 4 ng/mL	13 months

6.6.3 First-line hormonal treatment

Primary ADT has been the SOC for over 50 years [1034]. There is no high-level evidence in favour of a specific type of ADT for oncological outcomes, neither for orchiectomy nor for a LHRH agonist or antagonist. The level of testosterone is reduced much faster with orchiectomy and LHRH antagonist, therefore patients with impending spinal cord compression or other potential impending complications from the cancer should be treated with either a bilateral orchidectomy or LHRH antagonists as the preferred options.

There is a suggestion in some studies and a SR and meta-analysis that cardiovascular side effects are less frequent in patients treated with LHRH antagonists than patients treated with LHRH agonists [1053, 1097-1099]; therefore, patients with pre-existing cardiovascular disease or other cardiovascular risk factors might be considered to be treated with antagonists if a chemical castration is chosen.

6.6.3.1 Non-steroidal anti-androgen monotherapy

Based on a Cochrane review comparing older generation non-steroidal anti-androgen (NSAA) monotherapy to ADT (either medical or surgical), NSAA was considered to be less effective in terms of OS, clinical progression, treatment failure and treatment discontinuation due to AEs [1100] and is generally not recommended also because ADT-based combination treatments have become SOC.

6.6.3.2 Intermittent versus continuous androgen deprivation therapy

Three independent reviews [1101-1103] and two meta-analyses [1104, 1105] looked at the clinical efficacy of intermittent androgen deprivation (IAD) therapy. All of these reviews included eight RCTs of which only three were conducted in patients with exclusively M1 disease.

So far, the SWOG 9346 is the largest trial addressing IAD in M1b patients [1106]. Of 3,040 screened patients, only 1,535 patients met the inclusion criteria. This highlights that only about 50% of M1b patients can be expected to be candidates for IAD, i.e. the best PSA responders. This was a non-inferiority trial leading to inconclusive results: the actual upper limit was above the pre-specified 90% upper limit of 1.2 (HR: 1.1, CI: 0.99–1.23), the pre-specified non-inferiority limit was not achieved, and the results did not show a significant inferiority for any treatment arm. However, based on this study inferior survival with IAD cannot be completely ruled out even in this highly selected subgroup. The use of intermittent ADT has been superseeded as continuous ADT based combination therapy has become SOC.

6.6.3.3 Early versus deferred androgen deprivation therapy

Early treatment before the onset of symptoms is recommended in the majority of patients with metastatic hormone-sensitive disease despite lack of randomised phase III data in this specific setting and specifically not with the combination therapies that are standard nowadays.

A Cochrane analysis from 2019 about the topic concluded that early ADT probably extends time to death of any cause and time to death from PCa [1107]. Since the analysis included only a very limited number of metastatic patients, the benefit of early ADT in this setting remains unproven. All of the trials testing the combination therapies in the metastatic hormone-sensitive setting also included asymptomatic patients.

The only candidates with metastatic disease who may possibly be considered for deferred treatment are asymptomatic patients with a strong wish to avoid treatment-related side effects. The risk of developing symptoms, and even dying from PCa, without receiving the benefit from ADT with deferred treatment has been highlighted [1108, 1109], but in the era before next generation imaging was used.

Patients with deferred treatment for advanced PCa must be amenable to close follow-up. Another potential exception are patients with recurrent oligometastatic disease who have a strong wish to postpone the start of ADT (see Section 6.4.7).

6.6.4 ***Combination therapies***

All of the following combination therapies have been studied with continuous ADT, not intermittent ADT.

6.6.4.1 'Combined' androgen blockade with older generation NSAA (bicalutamide, flutamide, nilutamide)

Systematic reviews have shown that CAB using a NSAA appears to provide a small survival advantage (< 5%) vs. monotherapy (surgical castration or LHRH agonists) [1110, 1111] but this minimal survival advantage must be balanced against the increased side effects. In addition, the newer combination therapies (see Tables 6.4.3, 6.4.4, 6.4.5) are more effective as shown specifically for enzalutamide which was tested against NSAA in a phase III trial [1112]. More recently another trial has demonstrated a significant OS benefit for the addition of rezvilutamide vs. addition of bicalutamide to ADT in patients with high-volume mHSPC [1113]. Therefore combination with NSAAs should only be considered if other combination therapies are not available.

6.6.4.2 Androgen deprivation combined with other agents

6.6.4.2.1 Androgen deprivation therapy combined with chemotherapy

Three large RCTs were conducted [775, 1088, 1114]. All trials compared ADT alone as the SOC with ADT combined with immediate docetaxel (75 mg/sqm, every three weeks within three months of ADT initiation). The primary objective in all three studies was to assess OS. The key findings are summarised in Table 6.4.3.

Table 6.6.3: Key findings - Hormonal treatment combined with chemotherapy

	STAMPEDE [775, 1115]		**GETUG-AFU 15** [1114]		**CHAARTED** [1088, 1089]	
	ADT	ADT + Docetaxel (6 cycles) + P	ADT	ADT + Docetaxel (9 cycles)	ADT	ADT + Docetaxel (6 cycles)
N	1,184	592	193	192	393	397
Newly diagnosed M+	58%	59%	75%	67%	73%	73%
Key inclusion criteria	Patients scheduled for long-term ADT - newly diagnosed M1 or N+ situations - locally advanced (at least two of cT3 cT4, ISUP grade ≥ 4, PSA ≥ 40 ng/mL) - relapsing locally treated disease with a PSA > 4 ng/mL and a PSA-DT < 6 mo. or PSA > 20 ng/mL, or nodal or metastatic relapse		Metastatic disease Karnofsky score ≥ 70%		Metastatic disease ECOG PS 0, 1 or 2	

Primary objective	OS	OS	OS
Median follow up (mo)	43; 78.2 (update M1)	50	54 (update)
HR (95% CI)	0.78 (0.66-0.93)	1.01 (0.75-1.36)	0.72 (0.59-0.89)
M1 only			
N	1,086	-	-
HR (95% CI)	0.81 (0.69-0.95)	-	-

ADT = androgen deprivation therapy; CI = confidence interval; ECOG = Eastern Cooperative Oncology Group; HR = hazard ratio; ISUP = International Society for Urological Pathology; mo = month; n = number of patients; OS = overall survival; P = prednisone; PSA-DT = prostate-specific antigen-doubling time.

In the GETUG 15 trial, all patients had M1 PCa, either *de novo* or after a primary treatment [1114]. They were stratified based on previous treatment and Glass risk factors [1085]. In the CHAARTED trial the same inclusion criteria applied, and patients were stratified according to disease volume (see Table 6.4.1) [1088].

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), another was docetaxel combined with zoledronic acid (n = 593). Patients were included with either M1 or N1 or having two of the following three criteria: T3/4, PSA ≥ 40 ng/mL or ISUP grade group 4–5. Also relapsed patients after local treatment were included if they met one of the following criteria: PSA ≥ 4 ng/mL with a PSA-DT < six months or a PSA ≥ 20 ng/mL, N1 or M1. No stratification was used regarding metastatic disease volume (high/low volume) [775]. In all three trials toxicity was mainly haematological with around 12–15% grade 3–4 neutropenia, and 6–12% grade 3–4 febrile neutropenia. The use of granulocyte colony-stimulating factor receptor (GCSF) was shown to be beneficial in reducing febrile neutropenia. Primary or secondary prophylaxis with GCSF should be based on available guidelines [1116, 1117].

Docetaxel in all three trials was used at the standard dose of 75 mg/sqm every three weeks, six cycles in CHAARTED and STAMPEDE and up to nine cycles in GETUG-AFU-15. In subgroup analyses from GETUG-AFU 15 and CHAARTED the beneficial effect of the addition of docetaxel to ADT was most evident in men with *de novo* metastatic high-volume disease [1089, 1090], while it was in the same range whatever the volume in the *post-hoc* analysis from STAMPEDE [1115]. The effect of adding docetaxel was less apparent in men who had prior local radical treatment although the numbers were small and the event rates lower. A SR and meta-analysis which included these three trials showed that the addition of docetaxel to SOC improved survival [1117]. The HR of 0.77 (95% CI: 0.68–0.87, p < 0.0001) translates into an absolute improvement in 4-year survival of 9% (95% CI: 5–14). In a SR and meta-analysis of individual participant data from the the three trials it has been shown that there is no meaningful beneficial effect of addition of docetaxel to ADT for patients with metachronous low volume disease. Interestingly the largest absolute improvement at five years was observed for the patients with high volume and clinical stage four disease [1118].

Based on these data, upfront docetaxel combined with ADT was considered as a standard in men presenting with metastases at first presentation, provided they are fit enough to receive docetaxel [1117]. More recently two large Phase III studies have now shown an OS benefit by adding an ARPI to ADT and docetaxel. Therefore adding docetaxel alone to ADT should only be considered if no ARPI is available or all available ones are contraindicated (see Section 6.4.4.2.3).

6.6.4.2.2 Combination with an ARPI alone (abiraterone, apalutamide, enzalutamide)

In two large RCTs (STAMPEDE, LATITUDE) the addition of abiraterone acetate (1000 mg daily) plus prednisone (5 mg daily) to ADT in men with mHSPC was studied [814, 1070, 1119] (see table 6.4.4). The primary objective of both trials was an improvement in OS. Both trials showed a significant OS benefit. In LATITUDE with only *de novo* high-risk metastatic patients included, the HR reached 0.62 (0.51–0.76) [1070]. The HR in STAMPEDE was very similar with 0.63 (0.52–0.76) in the total patient population (metastatic and non-metastatic) and a HR of 0.61 in the subgroup of metastatic patients [814]. While only high-risk patients were included in the LATITUDE trial a *post-hoc* analysis from STAMPEDE showed the same benefit whatever the risk or the volume category was [1120].

All secondary objectives such as PFS, time to radiographic progression, time to pain, or time to chemotherapy were in favour of the combination. No difference in treatment-related deaths was observed with the combination of ADT plus AAP compared to ADT monotherapy (HR: 1.37 [0.82–2.29]). However, twice as many patients

discontinued treatment due to toxicity in the combination arms in STAMPEDE (20%) compared to LATITUDE (12%) [1119]. Based on these data upfront AAP combined with ADT should be considered as a standard in men presenting with metastases at first presentation, provided they are fit enough to receive the drug.

In three large RCTs (TITAN, ARCHES and ENZAMET) the addition of AR antagonists to ADT in men with mHSPC was tested [1068, 1069, 1112]. In ARCHES the primary endpoint was radiographic PFS (rPFS). In the primary analysis rPFS was significantly improved for the combination of enzalutamide and ADT with a HR of 0.39 (0.3–0.5). Approximately 36% of the patients had low-volume disease; around 25% had prior local therapy and 18% of the patients had received prior docetaxel. In the final prespecified analysis the key secondary enpoint OS was significantly improved with a HR of 0.66 (0.53-0.81) and a significant benefit for rPFS was maintained with a HR of 0.63 (0,52–0.76) [1121]. In ENZAMET the primary endpoint was OS. The addition of enzalutamide to ADT in the first analysis improved OS with a HR of 0.67 (0.52–0.86) compared to ADT plus a non-steroidal antiandrogen. Approximately half of the patients had concomitant docetaxel; about 40% had prior local therapy and about half of the patients had low-volume disease [1069]. In a planned later analysis with a median follow-up of 68 months the OS benefit of adding enzalutamide was maintained with a HR of 0.7 (0.58-0.84) [1122] In the TITAN trial, ADT plus apalutamide was used and rPFS and OS were co-primary endpoints. In the primary analysis rPFS was significantly improved by the addition of apalutamide with a HR of 0.48 (0.39–0.6); OS at 24 months was improved for the combination with a HR of 0.67 (0.51–0.89). In the final analysis the HR for OS was 0.65 (0.53–0.79) without adjustment for cross-over. In this trial 16% of patients had prior local therapy, 37% had low-volume disease and 11% received prior docetaxel [1068, 1123]. In the more recently published CHART trial, ADT plus rezvilutamide was tested vs. ADT plus bicalutamide in patients with high-volume *de novo* metastatic disease. Ninety percent of the patients were recruited in China. Overall survival and rPFS were co-primary endpoints. At the pre-planned interim analysis rezvilutamide significantly improved rPFS compared with bicalutamide with a HR of 0.44 (0.33–0.58) and OS with a HR of 0.58 (0.44–0.77) [1113].

In summary, the addition of the new AR antagonists significantly improves clinical outcomes with no convincing evidence of differences between subgroups. The majority of patients had *de novo* metastatic disease and the evidence is most compelling in this situation. In the trials with the new AR antagonists, a proportion of patients had metachronous disease (see Table 6.4.5); in the subgroup analyses the effect seemed to be consistent and therefore, a combination should also be offered for men progressing after radical local therapy [1122, 1124, 1125].

Table 6.6.4: Results from the STAMPEDE arm G and LATITUDE studies

	STAMPEDE [814]		**LATITUDE** [1070]	
	ADT	ADT + AA + P	ADT + placebo	ADT + AA + P
N	957	960	597	602
Newly diagnosed N+	20%	19%	0	0
Newly diagnosed M+	50%	48%	100%	100%
Key inclusion criteria	Patients scheduled for long-term ADT - newly diagnosed M1 or N+ situations - locally advanced (at least two of cT3 cT4, ISUP grade ≥ 4, PSA ≥ 40 ng/mL) - relapsing locally treated disease with a PSA > 4 ng/mL and a PSA-DT < 6 mo. or PSA > 20 ng/mL or nodal or metastatic relapse		Newly diagnosed M1 disease and 2 out of the 3 risk factors: ISUP grade ≥ 4, ≥ 3 bone lesions, measurable visceral metastasis	
Primary objective	OS		OS Radiographic PFS	
Median follow up (mo)	40		30.4	
3-yr. OS	83% (ADT + AA + P) 76% (ADT)		66% (ADT + AA + P) 49% (ADT + placebo)	
HR (95% CI)	0.63 (0.52-0.76)		0.62 (0.51-0.76)	

M1 only		
N	1,002	1,199
3-yr. OS	NA	66% (ADT + AA + P) 49% (ADT + placebo)
HR (95% CI)	0.61 (0.49-0.75)	0.62 (0.51-0.76)
HR	FFS (biological, radiological, clinical or death): 0.29 (0.25-0.34)	rPFS: 0.49 (0.39-0.53)

AA = abiraterone acetate; ADT = androgen deprivation therapy; CI = confidence interval; FFS = failure-free survival; HR = hazard ratio; ISUP = International Society of Urological Pathology; mo = month; n = number of patients; NA = not available; OS = overall survival; P = prednisone; rPFS = radiographic progression-free survival; PSA = prostate-specific antigen; yr. = year.

Table 6.6.5: Results from the ENZAMET and TITAN studies with OS as primary endpoint

	ENZAMET [1122]		**TITAN** [1068, 1123]	
	ADT+ older antagonist ± docetaxel (SOC)	ADT + enzalutamide ± docetaxel	ADT + placebo	ADT + apalutamide
N	562	563	527	525
Newly diagnosed M+	72.1%	72.5%	83.7%	78.3%
Low volume	47%	48%	36%	38%
Primary objective	OS		OS rPFS	
Median follow up (mo)	34		30.4	
3-yr. OS	3-yr survival: 80% (ADT + enzalutamide) 72% (SOC)		2-yr survival: 84% (ADT + apalutamide) 74% (ADT + placebo)	
HR (95% CI) for OS	0.67 (0.52-0.86)		0.67 (0.51-0.89)	

ADT = androgen deprivation therapy; CI = confidence interval; HR = hazard ratio; mo = month; n = number of patients; OS = overall survival; SOC = standard of care; rPFS = radiographic progression-free survival; yr = year.

Table 6.6.6: Results from the ARCHES and CHART studies [1069, 1113, 1121]

	ARCHES [1069, 1121]		**CHART** [1113]	
	ADT ± docetaxel	ADT + enzalutamide ± docetaxel	ADT + bicalutamide	ADT + rezvilutamide
N	576	574	328	326
Newly diagnosed M+	63%	70%	100%	100%
Low volume	35%	38%	0%	0%
Use of early docetaxel	18% (previous)	18% (previous)	0%	0%
Primary objective	rPFS		OS rPFS	
Median follow up (mo)	44.6		29.3	
Median rPFS (mo.)	38.9	49.8	23.5	Not reached
HR (95% CI) for rPFS	HR: 0.63 (0.52–0.76)		HR: 0.46 (0.36–0.60)	
Median OS	Not reached	Not reached	Not reached	Not reached
HR (95% CI) for OS	0.66 (0.53–0.81): Main secondary endpoint		0.58 (0.44–0.77)	

HR = hazard ratio; mo = month; n = number of patients; OS = overall survival; rPFS = radiographic progression-free survival; yr = year.

6.6.4.2.3 Combination with docetaxel and an ARPI

The addition of abiraterone to ADT and docetaxel has been reported to have a benefit in rPFS and in OS in the PEACE-1 trial [1126, 1127]. The trial has a 2x2 factorial design and participants with *de novo* (synchronous) metastatic PCa were randomised to SOC; at the beginning of the trial ADT, later ADT plus docetaxel for 6 cycles if chemotherapy-fit) vs. SOC plus radiotherapy vs. SOC plus abiraterone vs. SOC plus radiotherapy plus abiraterone. Co-primary endpoints were rPFS and OS, both were statistically significantly improved in the total population. Also in the group of patients who received ADT plus docetaxel as SOC (n = 710) both rPFS and OS were increased with a HR: 0.5 (0.34–0.71) and 0.75 (0.59–0.95), respectively. Of note; in this population about 35% had low-volume disease. Toxicity was modestly increased, mostly hypertension.

In the ARASENS Phase III trial all patients received ADT and docetaxel for 6 cycles as SOC plus darolutamide or placebo [1128]. 1,306 metastatic patients were included, 14 % of them with relapsed disease after radical local treatment (metachronous). Primary endpoint was OS and this was statistically significanty increased by the addition of darolutamide with a HR of 0.68 (0.57–0.8).

Interestingly, in this trial the occurrence of AEs was similar in both arms. In both trials docetaxel and the ARPI have been given concomitantly. Of the included patients 77% had high volume and 70% high-risk disease. In an unplanned subgroup analysis the beneficial effect of adding darolutamide versus placebo for OS was seen in the patients with high-volume (HR 0.69; 0.57-0.82), with high-risk (HR 0.71; 0.58-0.86) and in low-risk disease (HR 0.62; 0.42-0.9), for the small subgroup of patients with low-volume disease the results were suggestive of an OS benefit (HR 0.68; 0.41-1.13) [1129]

Also in ENZAMET, TITAN and ARCHES there were patients who received docetaxel as a part of SOC, thus not all concomitantly, but the percentage of patients receiving docetaxel in these trials was much lower [1068, 1069, 1112].

There are also SRs and network meta-analysis for systemic triplet therapies and they confirm that the triplets are more effective than ADT and docetaxel alone [1130], in one analysis looking into subgroups statistically significant for patients with high volume disease and *de novo* disease [1131].

*6.6.5 **Treatment selection and patient selection***

There have been several network meta-analyses of the published data concluding that combination therapy is more efficient than ADT alone, but none of the doublet combination therapies has been convincingly proven to be superior over another [1132-1137]. In a SR and meta-analysis looking at association between age and efficacy of combination therapy patients seemed to profit from combination therapy irrespective of age [1138]. As a consequence, patients should be offered combination treatment unless there are clear contra-indications or they present with asymptomatic disease and a very short life expectancy (based on non-cancer comorbidities).

Since the data of the above mentioned Phase III trials of the triplet therapies have been reported, docetaxel as sole addition to ADT is not longer a valid option in the majority of patients if an androgen receptor pathway inhibitor (ARPI) is available and there are no contra-indications to use one. From subgroup analysis of all the above-mentioned RCTs we know that probably all subgroups (high vs. low volume/risk and synchronous vs. metachronous) can profit from the addition of an ARPI to ADT. Therefore, in view of the current data the recommendation is using ADT plus ARPI as the sole additional therapy or the triplet with an ARPI plus docetaxel. Formally the question what the added value of adding docetaxel to ADT plus an ARPI has not been evaluated, but since triplet therapy seems not to add a lot of unexpected overlapping toxicities, the data should be discussed with patients who are fit for chemotherapy and an ARPI, realising that most of the toxicity is caused by adding the chemotherapy. There is more evidence for using the triplet in synchronous disease and the OS benefit in PEACE-1 seemed to be driven mostly by the high volume patients at the time point of the analysis for the publication, in ARASENS only few patients had low volume disease.

Of interest in some SRs and meta-analysis the authors found no significant difference for OS and/or PFS using the systemic triplet therapy compared to adding an ARPI alone to ADT [1135, 1139-1141]. In contrast one meta-analysis suggested a benefit of systemic triplet therapy versus ADT and ARPI and another meta-analysis showed a benefit in patients with high volume disease [1136, 1142]. In summary, the choice will most likely be driven by fitness for docetaxel, the nature of the disease (low/high volume; synchronous/metachronous), patient preference, the specific side effects, availability, logistics and cost.

*6.6.6 **Treatment of the primary tumour in newly diagnosed metastatic disease***

The first reported trial evaluating prostate RT in men with metastatic castration-sensitive disease was the HORRAD trial. Four hundred and thirty-two patients were randomised to ADT alone or ADT plus IMRT with IGRT to the prostate. Overall survival was not significantly different (HR: 0.9 [0.7–1.14]), median time to PSA progression was significantly improved in the RT arm (HR: 0.78 [0.63–0.97]) [1143]. The STAMPEDE trial evaluated 2,061 men with metastatic castration-sensitive PCa (mCSPC) who were randomised to ADT alone vs.

ADT plus RT to the prostate. This trial confirmed that RT to the primary tumour did not improve OS in unselected patients [1091]. However, following the results from CHAARTED and prior to analysing the data, the original screening investigations were retrieved, and patients categorised as low- or high volume. In the low-volume subgroup (n = 819) there was a significant OS benefit by the addition of prostate RT. This was confirmed by the latest analysis of long-term follow-up (median follow-up of 61 months [HR: 0.64 for OS benefit in the low-volume group]) [1144].

A secondary, not pre-planned analysis of the STAMPEDE trial confirmed the benefit of prostate RT in patients with ≤ 3 bone metastases, but also showed a benefit in patients with M1a disease [1145]. No evidence of difference in time to symptomatic local events was found with median follow-up of over five years [1144].The dose used in these indications should be equivalent of up to 72 Gy in 2 Gy fractions.

Therefore, RT of the prostate only in patients with low-volume metastatic disease should be considered. Of note, only 18% of these patients had additional docetaxel and no patients had additional AAP, so no clear recommendation can be made about triple combinations. In addition, it is not clear if these data can be extrapolated to RP as local treatment as results of ongoing trials are awaited.

In a SR and meta-analysis including the above two RCTs, the authors found that, overall, there was no evidence that the addition of prostate RT to ADT improved survival in unselected patients (HR: 0.92, 95% CI: 0.81–1.04, p = 0.195) [1146]. However, there was a clear difference in the effect of metastatic burden on survival with an absolute improvement of 7% in three-year survival in men who had four or fewer bone metastases.

*6.6.7 **Metastasis-directed therapy in M1-patients***

In patients relapsing after a local treatment, a metastases-targeting therapy has been proposed, with the aim to delay systemic treatment. In a retrospective analysis on 211 patients treated with MDT, Milenkovic *et al.* aimed at defining prognostic factors for MFS, palliative ADT-free (pADT) survival and cause-specific survival (CSS). With a median follow-up of 42 months after MDT, patients with cN1 only had significantly superior 5-years MFS, pADT and CSS when compared to patients with M1 disease (p<0.02). Of interest, 23% of patients were free of biochemical recurrence at five years [1147]. There are two randomised phase II trials testing metastasis-directed therapy (MDT) using surgery ± SABR vs. surveillance [1148] or SABR vs. surveillance in men with oligo-recurrent PCa [1149]. Oligo-recurrence was defined as < 3 lesions on choline-PET/CT only [1148] or conventional imaging with MRI/CT and/or bone scan [1149]. The sample size was small with 62 and 54 patients, respectively, and a substantial proportion of them had nodal disease only [1148]. Androgen deprivation therapy-free survival was the primary endpoint in one study which was longer with MDT than with surveillance [1148]. The primary endpoint in the ORIOLE trial was progression after six months which was significantly lower with SBRT than with surveillance (19% vs. 61%, p = 0.005) [1149].

Recently the combined results of STOMP and ORIOLE confirmed the significant improvement in PFS in favour of MDT (HR: 0.44, p < 0.001) [1150].

A phase II trial assessed the biochemical response after ^{18}F-DCFPyL PET/MRI and subsequent MDT. Overall biochemical response rate, defined as ≥ 50% PSA decline, was 60%, including 22% of patients with complete biochemical response [1151].

Currently there are no data to suggest an improvement in OS. Two comprehensive reviews highlighted MDT (SABR) as a promising therapeutic approach that must still be considered as investigational until the results of the ongoing RCT are available [1152, 1153]. Thus far, the toxicity of MDT appears to be low, but this also needs to be confirmed [1154, 1155].

*6.6.8 **Guidelines for the first-line treatment of hormone-sensitive metastatic disease****

Recommendations	Strength rating
Offer immediate systemic treatment with androgen deprivation therapy (ADT) to palliate symptoms and reduce the risk for potentially serious sequelae of advanced disease (spinal cord compression, pathological fractures, ureteral obstruction) to M1 symptomatic patients.	Strong
Offer short-term administration of an older generation androgen receptor (AR) antagonist to M1 patients starting LHRH agonist to reduce the risk of the 'flare-up' phenomenon.	Weak
At the start of ADT offer luteinising hormone-releasing hormone (LHRH) antagonists or orchiectomy to patients with impending clinical complications such as spinal cord compression or bladder outlet obstruction.	Strong
Do not offer AR antagonist monotherapy to patients with M1 disease.	Strong

Do not offer ADT monotherapy to patients whose first presentation is M1 disease if they have no contra-indications for combination therapy and have a sufficient life expectancy to benefit from combination therapy (≥ 1 year) and are willing to accept the increased risk of side effects.	Strong
Offer ADT combined with abiraterone acetate plus prednisone or apalutamide or enzalutamide to patients with M1 disease who are fit for the regimen.	Strong
Offer docetaxel only in combination with ADT plus abiraterone or darolutamide to patients with M1 disease who are fit for docetaxel.	Strong
Offer ADT combined with prostate radiotherapy (using doses up to the equivalent of 72 Gy in 2 Gy fractions) to patients whose first presentation is M1 disease and who have low volume of disease by CHAARTED criteria.	Strong
Do not offer ADT combined with surgery to M1 patients outside of clinical trials.	Strong
Only offer metastasis-directed therapy to M1 patients within a clinical trial setting or a well-designed prospective cohort study.	Strong

**All the following statements are based on metastatic disease defined by bone scintigraphy and CT scan/MRI.*

6.7 Treatment: Castration-resistant PCa (CRPC)

*6.7.1 **Definition of CRPC***

Castrate serum testosterone < 50 ng/dL or 1.7 nmol/L plus either:

a. Biochemical progression: Three consecutive rises in PSA at least one week apart resulting in two 50% increases over the nadir, and a PSA > 2 ng/mL or

b. Radiological progression: The appearance of new lesions: either two or more new bone lesions on bone scan or a soft tissue lesion using RECIST (Response Evaluation Criteria in Solid Tumours) [1156]. Symptomatic progression alone must be questioned and subject to further investigation. It is not sufficient to diagnose CRPC.

*6.7.2 **Management of mCRPC - general aspects***

Selection of treatment for mCRPC is multifactorial and in general dependent on:

- previous treatment for mHSPC and for non-mHSPC;
- previous treatment for nmCRPC and mCRPC;
- quality of response and pace of progression on previous treatment;
- known cross resistance between androgen receptor pathway inhibitor (ARPI);
- co-medication and known drug interactions (see approved summary of product characteristics);
- known genetic alterations and microsatellite instability–high (MSI-H)/mismatch repair–deficient (dMMR) status;
- known histological variants and DNA repair deficiency (to consider platinum or targeted therapy like PARPi);
- local approval status of drugs and reimbursement situation;
- available clinical trials;
- The patient and his comorbidities.

6.7.2.1 Molecular diagnostics

All metastatic patients should be offered somatic genomic testing for homologous repair and MMR defects early on, preferably before firstline mCRPC treatment is established. Testing should preferably be performed on metastatic carcinoma tissue but testing on primary tumour may also be performed. Alternatively, but still less common, genetic testing on circulating tumour DNA (ctDNA) is an option and has been used in some trials. One test, the FoundationOne® Liquid CDx, has been FDA approved [1157]. Defective *MMR* assessment can be performed by IHC for MMR proteins (MSH2, MSH6, MLH1 and PMS2) and/or by next generation sequencing (NGS) assays [1158]. Germline testing for *BRCA1/2*, *ATM* and *MMR* is recommended for high-risk- and particularly for metastatic PCa if clinically indicated.

Molecular diagnostics should be performed by a certified (accredited) institution using a standard NGS multiplication procedure (minimum depth of coverage of 200 X). The genes and respective exons should be listed; not only DNA for mutations but RNA needs to be examined for fusions and protein expression to obtain all clinically relevant information. A critical asset is the decision support helping to rate the mutations according to their clinical relevance [1159, 1160].

Level 1 evidence for the use of PARP-inhibitors has been reported [248, 1161, 1162]. Microsatellite instability (MSI)-high (or *MMR* deficiency) is rare in PCa, but for those patients, pembrolizumab has been approved by the FDA and could be a valuable additional treatment option [1080, 1163]. Germline molecular testing is discussed in Section 5.1.6 - Genetic testing for inherited PCa. Recommendations for germline testing are provided in Section 5.1.7.

6.7.3 Treatment decisions and sequence of available options

Approved agents for the treatment of mCRPC in Europe are docetaxel, abiraterone/prednisolone (AAP), enzalutamide, cabazitaxel, olaparib, niraparib/AAP, talazoparib/enzalutamide, radium-223 and lutetium (^{177}Lu) vipivotide tetraxetan. Regarding CRPC, darolutamide and apalutamide have been approved only for nmCRPC. In general, sequencing of ARPIs like abiraterone and enzalutamide is not recommended particularly if the time of response to ADT and to the first ARPI was short (≤ six to twelve months) and high-risk features of rapid progression are present (see detailed discussion in Section 6.7.7) [1164, 1165].

The use of chemotherapy with docetaxel and subsequent cabazitaxel in the treatment sequence is recommended and should be applied early enough when the patient is still fit for chemotherapy. This is supported by high-level evidence [1164].

6.7.4 Non-metastatic CRPC

Frequent PSA testing in men treated with ADT has resulted in earlier detection of biochemical progression. Of these men approximately one-third will develop bone metastases within two years, detected by conventional imaging [893].

In men with CRPC and no detectable clinical metastases using bone scan and CT-scan, baseline PSA level, PSA velocity and PSA-DT have been associated with time to first bone metastasis, bone MFS and OS [893, 1166]. 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 suggested a bone scan and a CT scan when the PSA reached 2 ng/mL and if this was negative, it should be repeated when the PSA reached 5 ng/mL, and again after every doubling of the PSA based on PSA testing every three months in asymptomatic men [1167]. Symptomatic patients should undergo relevant investigations regardless of PSA level. With more sensitive imaging techniques like PSMA PET/CT or whole-body MRI, more patients are diagnosed with early mCRPC [1168]. It remains unclear if the use of PSMA PET/CT in this setting improves outcome.

Three large phase III RCTs, PROSPER [1169] , SPARTAN [1170] and ARAMIS [1171] , evaluated MFS as the primary endpoint in patients with nmCRPC (M0 CRPC) treated with enzalutamide (PROSPER) vs. placebo or apalutamide (SPARTAN) vs. placebo or darolutamide (ARAMIS) vs. placebo ,respectively (see Table 6.7.1). The M0 status was established by CT and bone scans. Only patients at high risk for the development of metastasis with a short PSA-DT of ≤ ten months were included. Patient characteristics in the trials revealed that about two-thirds of participants had a PSA-DT of < six months. All trials showed a significant MFS benefit. All three trials showed a survival benefit after a follow-up of more than 30 months. In view of the long-term treatment with these AR targeting agents in asymptomatic patients, potential AEs need to be taken into consideration and the patient informed accordingly.

Table 6.7.1: Randomised phase III controlled trials – nmCRPC

Study	Intervention	Comparison	Selection criteria	Main outcomes
ARAMIS 2019, 2020 [1171, 1172]	ADT + darolutamide	ADT + placebo	nmCRPC; baseline PSA ≥ 2 ng/mL PSA-DT ≤ 10 mo.	**59% reduction of distant progression or death** **Median MFS: darolutamide 40.4 vs placebo 18.4 mo;** **31% reduction in risk of death** HR = 0.69 (95% CI: 0.53–0.88) p = 0.003
PROSPER 2018, 2020 [1169, 1173]	ADT + enzalutamide	ADT + placebo	nmCRPC; baseline PSA ≥ 2 ng/mL PSA-DT ≤ 10 mo.	**71% reduction of distant progression or death** **Median MFS: enzalutamide 36.6 vs placebo 14.7 months;** **27% reduction in risk of death** HR = 0.73 (95% CI: 0.61–0.89) p = 0.001

SPARTAN 2018, 2021 [1170, 1174]	ADT + apalutamide	ADT + placebo	nmCRPC; baseline PSA ≥ 2 ng/mL PSA-DT ≤ 10 mo.	**72% reduction of distant progression or death** **Median MFS: apalutamide 40.5 vs placebo 16.2 months;** **22% reduction in risk of death** HR = 0.78 (95% CI: 0.64–0.96) p = 0.0161

ADT = androgen-deprivation therapy; CI = confidence interval; HR = hazard ratio; MFS = metastasis-free survival; nmCRPC = non-metastatic castrate-resistent prostate cancer; PSA-DT = prostate-specific antigen doubling time.

*6.7.5 **Metastatic CRPC***

The remainder of this section focuses on the management of men with proven mCRPC on conventional imaging.

6.7.5.1 Conventional androgen deprivation in CRPC

Eventually men with PCa will show evidence of disease progression despite castration. Two trials have shown only a marginal survival benefit for patients remaining on LHRH analogues during second- and thirdline therapies [1175, 1176]. However, in the absence of prospective data, the modest potential benefits of continuing castration outweigh the minimal risk of treatment. In addition, all subsequent treatments have been studied in men with ongoing androgen suppression, therefore, it should be continued in these patients.

*6.7.6 **First-line treatment of metastatic CRPC***

6.7.6.1 Abiraterone

Abiraterone was evaluated in 1,088 chemo-naive, asymptomatic or mildly symptomatic mCRPC patients in the phase III COU-AA-302 trial. Patients were randomised to abiraterone acetate or placebo, both combined with prednisone [1177]. Patients with visceral metastases were excluded. The main stratification factors were ECOG PS 0 or 1 and asymptomatic or mildly symptomatic disease. Overall survival and 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) [1178]. Adverse events related to mineralocorticoid excess and liver function abnormalities were more frequent with abiraterone, but mostly grade 1–2. Subset analysis of this trial showed the drug to be equally effective in an elderly population (> 75 years) [1179].

6.7.6.2 Enzalutamide

A randomised phase III trial (PREVAIL) included a similar patient population and compared enzalutamide and placebo [1180]. Men with visceral metastases were eligible but the numbers included were small. Corticosteroids were allowed but not mandatory. PREVAIL was conducted in a chemo-naive mCRPC population of 1,717 men and showed a significant improvement in both co-primary endpoints, rPFS (HR: 0.186, CI: 0.15–0.23, p < 0.0001), and OS (HR: 0.706, CI: 0.6–0.84, p < 0.001). A ≥ 50% decrease in PSA was seen in 78% of patients. The most common clinically relevant AEs were fatigue and hypertension. Enzalutamide was equally effective and well tolerated in men > 75 years [1181] as well as in those with or without visceral metastases [1182]. However, for men with liver metastases, there seemed to be no discernible benefit [1182, 1183].

Enzalutamide has also been compared with bicalutamide 50 mg/day in a randomised double-blind phase II study (TERRAIN) showing a significant improvement in PFS (15.7 months vs. 5.8 months, HR: 0.44, p < 0.0001) in favour of enzalutamide [1183]. With extended follow-up and final analysis the benefit in OS and rPFS were confirmed [1184].

6.7.6.3 Docetaxel

A statistically significant improvement in median survival of 2.0–2.9 months has been shown with docetaxel based chemotherapy compared to mitoxantrone plus prednisone [1185, 1186]. The standard first-line chemotherapy is docetaxel 75 mg/m^2, three-weekly doses combined with prednisone 5 mg twice a day (BID), up to ten cycles. Prednisone can be omitted if there are contra-indications or no major symptoms. The following independent prognostic factors: visceral metastases, pain, anaemia (Hb < 13 g/dL), bone scan progression, and prior estramustine may help stratify the response to docetaxel. Patients can be categorised into three risk groups: low risk (0 or 1 factor), intermediate (2 factors) and high risk (3 or 4 factors), and show three significantly different median OS estimates of 25.7, 18.7 and 12.8 months, respectively [1187].

Age by itself is not a contra-indication to docetaxel [1188] but attention must be paid to careful monitoring and comorbidities as discussed in Section 5.4 - Estimating life expectancy and health status [1189].

In men with mCRPC who are thought to be unable to tolerate the standard dose and schedule, docetaxel 50 mg/m^2 every two weeks seems to be well tolerated with less grade 3–4 AEs and a prolonged time to treatment failure [1190].

6.7.6.4 Sipuleucel-T

In 2010 a phase III trial of sipuleucel-T showed a survival benefit in 512 asymptomatic or minimally symptomatic mCRPC patients [1191]. 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, with a HR of 0.78 (p = 0.03). No PSA decline was observed and PFS was similar 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. Sipuleucel-T is not available in Europe.

6.7.6.5 Ipatasertib

The AKT inhibitor ipatasertib in combination with AAP was studied in asymptomatic or mildly symptomatic patients with and without PTEN loss by IHC and previously untreated for mCRPC. The randomised phase III trial (IPAtential) showed a significant benefit for the first endpoint rPFS in the PTEN loss (IHC) 18.5 vs. 16.5 mo; p = 0.0335, HR: 0.77, 95% CI: 0.61–0,98) but not in the intention to treat (ITT) population. The OS results are still pending. Side effects of the AKT inhibitor ipatasertib include rash and diarrhoea [1077]. Grade 3 or higher AEs occurred nearly double as often in the combination group and the discontinuation rate due to AEs was four times higher. This combination is still investigational [1192].

6.7.6.6 Combinations with PARP inhibitors

Based on the suggestion that there is a synergistic antitumour effect when combining an ARPI with a PARP inhibitor, several such combination trials were conducted in first-line mCRPC patients with different trial designs, different patient selection and conflicting results.

Abiraterone/prednisone plus olaparib

A randomised double-blind, phase III trial (PROpel) of AAP plus olaparib (300 mg twice daily) or placebo in patients with mCRPC in the first-line setting was conducted [1193, 1194]. Patients (n=796) were randomly assigned 1:1 to study treatment regardless of homologous recombination repair gene mutation (HRRm) status which was retrospectively evaluated and determined by tumour tissue and circulating tumour DNA tests. The primary end point was imaging-based PFS (ibPFS) by investigator assessment. The result was significantly positive in favour of the combination with ibPFS of 24.8 vs. 16.6 mo (HR 0.66; 95% CI: 0.54 to 0.81; p = 0.001). In the prespecified final analyses the key secondary endpoint OS had only 47.9% maturity and did not meet the prespecified 2-sided boundary for significance (HR 0.95% CI: 0.81, 0.67-1.0, p= 0,054).The subgroup of patients with positive HRRm status showed a rPFS HR of 0.50 (CI: 0.34 to 0.73). The BRCA mutated patients (11% of the ITT population) had an even larger benefit for rPFS (HR 0.24; 95% CI: 0.12, 0.45) and the OS HR in these patients was 0.30 (95% CI: 0.15, 0.59), suggesting that the improvement in rPFS observed in the ITT population was primarily driven by patients with a BRCA mutation [1195].

The most common AEs in patients receiving olaparib plus AAP were anaemia (48%; ≥G3 15%; at least one blood transfusion in 18%; multiple transfusions 12% [1195]. The most common adverse reactions with olaparib plus abiraterone were anaemia (48%), fatigue (38%), nausea (30%), diarrhoea (19%), decreased appetite (16%), lymphopenia (14%), dizziness (14%), and abdominal pain (13%); 18% of patients required at least one blood transfusion and 12% required multiple transfusions. The combination of olaparib plus AAP was approved by the EMA for the treatment of adult patients with mCRPC in whom chemotherapy is not clinically indicated [1240]. In the US, the FDA has approved olaparib with AAP for mCRPC patients with deleterious or suspected deleterious BRCA-mutations as determined by an FDA-approved companion diagnostic test [1197].

Abiraterone/prednisone plus niraparib

In a randomised, double-blind, phase III trial (MAGNITUDE) AAP plus niraparib 200 mg once/daily or placebo, was evaluated [1198]. The study prospectively included 2 cohorts, an HRR-negative and an HRR-positive cohort. The HRR-negative cohort was closed early for futility after enrolling 200 patients. In the overall HRR-positive cohort, the addition of Niraparib to AAP resulted in a significant improvement in the first endpoint rPFS compared to AAP plus placebo (HR = 0.73; 95% CI 0.56-0.96; p = 0.0217) and the median rPFS was 16.5 vs. 13.7 months in favour of the combination. In particular, the 113 patients with BRCA 1/ 2 mutations [1199] who received AAP plus niraparib [1199] derived a major rPFS benefit (19.5 versus 10.9 months; HR = 0.55 [95% CI 0.39-0.78]; nominal p = 0.0007). The OS data is still immature. The most common side effects with Niraparib plus AAP in the ITT population were anemia (46.2%), fatigue (26.4%), hypertension (31.6%) and constipation (30.7%). The combination of niraparib plus AAP in a dual-action tablet has been approved by the EMA and the FDA for patients with mCRPC and BRCA 1/2 mutations in whom chemotherapy is not clinically indicated [1200].

Enzalutamide plus Talazoparib

A randomised double-blind, phase III trial (TALAPRO-2) of the PARP inhibitor talazoparib (0.5mg daily) plus enzalutamide versus enzalutamide/placebo showed a significantly better median rPFS (first endpoint) in favour of the combintion regardless of homologous recombination repair pathway status [1202].

The median was not yet reached for the combination as compared to 21.9 mo in the control arm (95% CI 16.6-25.1). The HR for rPFS was 0.63 (0.51-0.78) with p<0.0001. For the subgroups of patients with HRR mutations the benefit of the combination was much more pronounced. The HRR gene-mutated population showed a median rPFS of 27.9 (16.6–not reached) for the talazoparib combination versus 16.4 (10.9–24.6) for the placebo group (0.46; 95% CI: 0.30–0.70; p=0.0003) and 0.70 (0.54–0.89; p=0.0039) in patients with a status of non-deficient or unknown. In an exploratory analysis, the HR for rPFS in patients with BRCA-mutated mCRPC was 0.23 (0.10–0.53; p=0.0002) and, in patients with non-BRCAm HRR gene-mutated mCRPC, it was 0.66 (0.39–1.12; p=0.12) in favour of the talazoparib combination.[1202] The OS data are still immature. The expected clinical benefit in the subgroups needs to be weighed against the potential burden of side effects.

The most common treatment-emergent adverse events with the addition of talazoparib were anaemia, neutropenia, and fatigue; the most common grade 3–4 event was anaemia (46%), which improved after dose reduction, however, 39% required a blood transfusion, including 22% who required multiple transfusions, 8% discontinued treatment due to anemia and 2 patients on the combination were diagnosed with myelodysplastic syndrome/acute myeloid leukemia [1202]. In TALAPRO-2 also an HRR-deficient-only cohort (cohort 2; N = 230) was recruited. The primary analysis for the combined HRR-deficient population (N = 399) met the rPFS endpoint with a HR 0.45 (95% CI, 0.33 to 0.61; P < 0.0001; median not reached at the time of the analysis for the talazoparib group versus 13.8 months for the placebo group). Also for this cohort data for OS are immature but favor talazoparib (HR 0.69; 95% confidence interval, 0.46 to 1.03; P = 0.07) [1203].

The FDA approved talazoparib with enzalutamide only for HRR gene-mutated mCRPC [1201]. The European commission approved talazoparib with enzalutamide for the treatment of patients with mCRPC (with or without gene mutations) in whom chemotherapy is not clinically indicated.

Table 6.7.2: Randomised phase III controlled trials - first-line treatment of mCRPC

Study	Intervention	Comparison	Selection criteria	Main outcomes
DOCETAXEL				
SWOG 99-16 2004 [1204]	docetaxel/EMP, every 3 weeks, 60 mg/m^2, EMP 3 x 280 mg/day	mitoxantrone, every 3 weeks, 12 mg/m^2 prednisone 5 mg BID		**OS: 17.52 vs. 15.6 mo.** (p = 0.02, HR: 0.80; 95% CI: 0.67-0.97) **PFS: 6.3 vs. 3.2 mo.** (p < 0.001)
TAX 327 2004, 2008 [1185, 1186]	docetaxel, every 3 weeks, 75 mg/m^2 prednisone 5 mg BID or docetaxel, weekly, 30 mg/m^2 prednisone 5 mg BID	mitoxantrone, every 3 weeks, 12 mg/m^2, Prednisone 5 mg BID		**OS: 19.2 for 3 weekly vs. 17.8 mo. 4-weekly and 16.3 in the control group.** (p = 0.004, HR: 0.79, 95% CI: 0.67-0.93)
ABIRATERONE				
COU-AA-302 2013, 2014, 2015 [1177, 1178, 1205]	abiraterone + prednisone	placebo + prednisone	- No previous docetaxel. - ECOG 0-1. - PSA or radiographic progression. - No or mild symptoms. - No visceral metastases.	**OS: 34.7 vs. 30.3 mo.** (HR: 0.81, p = 0.0033). **FU: 49.2 mo. rPFS: 16.5 vs. 8.3 mo.** (p < 0.0001)
ENZALUTAMIDE				
PREVAIL 2014 [1180]	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 < 0.001). FU: 22 mo. (p < 0.001 HR: 0.71, 95% CI: 0.60-0.84) **rPFS: 20.0 mo. vs. 5.4 mo.** HR: 0.186 (95% CI: 0.15-0.23) p < 0.0001)

SIPULEUCEL-T				
IMPACT 2010 [1191]	sipuleucel-T	placebo	- 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)
2006 [1206]	sipuleucel-T	placebo	- ECOG 0-1. - No visceral met. - No corticosteroids.	**OS: 25.9 vs. 21.4 mo.** (p = 0.1). FU: 36 mo. **PFS: 11.7 vs. 10.0 wk.**
IPATASERTIB				
IPAtential150 2021 [1192]	ipatasertib (400 mg/d) + abiraterone (1000 mg/d) + prednisone (5 mg bid)	abiraterone + prednisolone + placebo	Previously untreated for mCRPC, asymptomatic/ mildly symptomatic, with and without PTEN loss by IHC	**rPFS in PTEN loss (IHC) population: 18.5 vs. 16.5 mo.** (p = 0.0335, HR: 0.77 95% CI: 0.61-0.98)
COMBINATIONS				
PROpel [1193, 1194]	olaparib (300mg BID) + abiraterone (1000 mg/d) + prednisone (5 mg BID)	placebo + abiraterone + prednisone	-ECOG 0-1 - regardless of HRRm (retrospective testing) - prior taxane for mHSPC allowed	**ibPFS in ITT population: 24.8 vs. 16.6 mo;** HR: 0.66; 95% CI: 0.54–0.81; (p = 0.001) ibPFS in BRCA+: HR 0.24; 95% CI: 0.12-0.45
				OS in ITT population: 42.1 vs. 34.7 mo; HR 0.81; 95% CI: 0.67-1.0; (p= 0.054) OS in BRCA+: HR 0.29; 95% CI: 0.15- 0.56
MAGNITUDE [1199, 1207]	niraparib 200 mg/d + abiraterone (1000 mg/d plus prednisone 5 mg BID)	placebo + abiraterone (1,000 mg/d plus prednisone 5 mg BID)	- ECOG 0-1 - AAP ≤ 4mo allowed for mCRPC; - HRR-biomarker positive cohort - prior docetaxel for mHSPC allowed - prior ARPI for mHSPC allowed - prior ARPI for mCRPC allowed	**rPFS (central review) in HRR+: 16.5 vs. 13.7 mo** HR = 0.73; 95% CI: 0.56-0.96; (p = 0.022) **rPFS (central review) in BRCA 1/ 2+: 16.5 vs. 13.7 mo** rPFS 19.5 versus 10.9 months; HR= 0.55; 95% CI 0.39-0.78; (nominal p= 0.0007)
TALAPRO-2 [1202]	talazoparib (0.5mg/d) + enzalutamide 160mg/d	enzalutamide + placebo	- ECOG 0-1 - All-comers: HHR deficient and HRR non-deficient or unknown -prior AAP or docetaxel allowed for mHSPC	**rPFS in ITT: NR (27.5-NR) vs. 21.9 mo;** HR 0.63; 95% CI: 0.51-0.78 (p<0.0001); rPFS in BRCA+: HR 0·23; 95% CI: 0.10–0.53; p=0·0002

BID = twice a day; CI = confidence interval; ECOG = Eastern Cooperative Oncology Group; EMP = estramustine; FU = follow-up; HR = hazard ratio; mets. = metastases; mo = month; ib (imaging based); (r)PFS = (radiographic) progression-free survival; OS = overall survival; IHC = immunohistochemistry ; HRRm = homologour recombination repair genes mutation; BRCA+ = BRCA gene mutated; ITT = intention to treat; BICR = blinded independent central review.

*6.7.7 **Second-line treatment for mCRPC***

All patients who receive treatment for mCRPC will eventually progress. All treatment options in this setting are presented in Table 6.7.3. High-level evidence exists for second-line treatments after first-line treatment for mCRPC with docetaxel or with ARPI. There is a paucity of high-level data with regards to the sequence of treatments in case of pretreatment with ARPI and/or docetaxel for mHSPC.

6.7.7.1 Cabazitaxel

Cabazitaxel is a taxane with activity in docetaxel-resistant cancers. It was studied in a large prospective, randomised, phase III trial (TROPIC) comparing cabazitaxel plus prednisone vs. mitoxantrone plus prednisone in 755 patients with mCRPC, who had progressed after or during docetaxel-based chemotherapy [1208]. Patients received a maximum of ten cycles of cabazitaxel (25 mg/m^2) or mitoxantrone (12 mg/m^2) plus prednisone (10 mg/day). Overall survival was the primary endpoint 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. In two post-marketing randomised phase III trials, cabazitaxel was shown not to be superior to docetaxel in the first-line setting; in the second-line setting in terms of OS, 20 mg/m^2 cabazitaxel was not inferior to 25 mg/m^2, but less toxic. Therefore, the lower dose should be preferred [1209, 1210]. Cabazitaxel should preferably be given with prophylactic granulocyte colonystimulating factor (G-CSF) and should be administered by physicians with expertise in handling neutropenia and sepsis [1211].

6.7.7.2 Abiraterone acetate after docetaxel

Positive results of the large phase III trial (COU-AA-301) were reported after a median follow-up of 12.8 months [1212] and confirmed by the final analysis [1213]. A total of 1,195 patients with mCRPC were randomised 2:1 to AAP or placebo plus prednisone. All patients had progressive disease based on the Prostate Cancer Clinical Trials Working Group 2 (PCWG2) criteria after docetaxel therapy (with a maximum of two previous chemotherapeutic regimens). The primary endpoint was OS, with a planned HR of 0.8 in favour of AAP. After a median follow-up of 20.2 months, the median survival in the AAP 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 AAP (PSA, radiologic tissue response, time to PSA or objective progression). The incidence of the most common grade 3–4 AEs did not differ significantly between arms, but mineralocorticoid-related side effects were more frequent in the AAP group, mainly grade 1–2 (fluid retention, oedema and hypokalaemia).

6.7.7.3 Enzalutamide after docetaxel

The planned interim analysis of the AFFIRM study was published in 2012 [1214]. 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 about 30% of the patients. The primary endpoint 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 to halt and unblind the study. The benefit was observed irrespective of age, baseline pain intensity, and type of progression. In the final analysis with longer follow-up the OS results were confirmed despite crossover and extensive post-progression therapies [1160]. Enzalutamide was active also in patients with visceral metastases.

All the secondary objectives were in favour of enzalutamide (PSA, soft tissue response, QoL, time to PSA, or objective progression). No difference in terms of side effects was observed in the two groups, with a lower incidence of grade 3–4 AEs in the enzalutamide arm. There was a 0.6% incidence of seizures in the enzalutamide group compared to none in the placebo arm.

6.7.7.4 Radium-223 after ARPI or both ARPI and docetaxel

The only bone-specific drug that is associated with a survival benefit is the α-emitter radium-223. In a large phase III trial (ALSYMPCA) 921 patients with symptomatic mCRPC, who failed or were unfit for docetaxel, were randomised to six injections of 50 kBq/kg radium-223 or placebo plus SOC. The primary endpoint was OS. Radium-223 significantly improved median OS by 3.6 months (HR: 0.70, $p < 0.001$) and was also associated with prolonged time to first skeletal event, improvement in pain scores and improvement in QoL [1215]. The associated toxicity was mild and, apart from slightly more haematologic toxicity and diarrhoea with radium-223, which did not differ significantly from that in the placebo arm [1215]. Radium-223 was effective and safe whether or not patients were docetaxel pre-treated [1216]. Due to safety concerns, use of radium-223 was

restricted to after docetaxel and at least one AR targeted agent [1217]. In particular, the use of radium-223 in combination with AAP showed significant safety risks related to fractures and more deaths. This was most striking in patients without the concurrent use of bone health agents [1218] so that radium-223 should always be used together with bone health agents (see chapter 6.7.11.2)

6.7.7.5 Rucaparib after ARPI [1219]

In a 2:1 randomised, controlled, phase III trial (TRITON-3) 405 mCRPC patients were included. Patients were selected for a *BRCA1*, *BRCA2*, or ATM alteration and disease progression after treatment with an ARPI for mCRPC. Treatment was as follows: rucaparib 600 mg twice daily or a physician's choice control, either second line docetaxel or the ARPI which had not been given previously. The first endpoint rPFS in the intention-to-treat group was significantly better with rucaparib (median, 10.2 months and 6.4 months, respectively; HR 0.61; 95% CI, 0.47 to 0.80; p<0.001). The small ATM subgroup did not derive abenefit. An interim analysis revealed OS to be immature. The study designed allowed for cross-over and 60% of patients received a PARP inhibitor at progression (47% rucaparib). With regards to the control arms, the median rPFS was longer with rucaparib than with docetaxel (11.2 months vs. 8.3 months; hazard ratio, 0.53; 95% CI, 0.37 to 0.77) and it was also longer than with an ARPI (11.2 months vs. 4.5 months; hazard ratio, 0.38; 95% CI, 0.25 to 0.58). The most frequent adverse events with rucaparib were fatigue, nausea and anemia, including 24% Grade ≥3 anemia and 29% of patients on rucaparib required at least one blood transfusion [1220]. Rucaparib has been approved by the FDA.

6.7.7.6 Olaparib after ARPI (see chapter 6.7.8.3 PARP inhibitors for mCRPC)

*6.7.8 **Treatment after docetaxel and one line of hormonal treatment for mCRPC***

6.7.8.1 General considerations

For men progressing quickly on AR targeted therapy (< twelve months) it is now clear that cabazitaxel is the treatment supported by the best data. The CARD trial, an open label randomised phase III trial, evaluated cabazitaxel after docetaxel and one line of ARPI (either AAP or enzalutamide) [1164]. It included patients progressing in less than twelve months on previous abiraterone or enzalutamide for mCRPC. Cabazitaxel more than doubled rPFS vs. another ARPI and reduced the risk of death by 36% vs. ARPI. The rPFS with cabazitaxel remained superior regardless of the ARPI sequence and if docetaxel was given before, or after, the first ARPI.

The choice of further treatment after docetaxel and one line of HT for mCRPC is open for patients who have a > twelve months response to first-line abiraterone or enzalutamide for mCRPC [1184]. Either second-line chemotherapy (cabazitaxel), radium-223 (if bone-only metastases), 177Lu–PSMA-617 radioligand therapy [1221, 1222] and PARP inhibitors (if BRCA mutation) are valuable options.

Men previously treated with at least one ARPI or both an ARPI and docetaxel and whose tumours demonstrated homozygous deletions or deleterious mutations in DNA-repair genes showed an 88% response rate to olaparib [1223] and in another confirmatory trial a composite response of 54.3% (95% CI: 39.0–69.1) in the 400 mg cohort and in 18 of 46 (39.1%; 25.1–54.6) evaluable patients in the 300 mg cohort [1224]. See also section 'Second-line management'). In general, subsequent treatments in unselected patients are expected to have less benefit than with earlier use [1225, 1226] and there is evidence of cross-resistance between enzalutamide and abiraterone [1227, 1228].

6.7.8.2 Radiopharmaceuticals

6.7.8.2.1 Introduction

Historically, several radiopharmaceuticals including phosphorous-32, strontium-89, yttrium-90, samarium-153, and rhenium-186 were developed for the treatment of bone pain secondary to metastases from PCa [1229]. They proved effective in a palliation setting, by relieving pain and improving QoL, especially in the setting of diffuse bone metastases. However, they never gained widespread adoption. The first radioisotope to demonstrate a survival benefit was radium-223 (see Section 6.7.7.4).

6.7.8.2.2 PSMA-based therapy

The increasing use of PSMA PET as a diagnostic tracer and the realisation that this allowed identification of a greater number of metastatic deposits led to attempts to treat cancer by replacing the imaging isotope with a therapeutic isotope which accumulates where the tumour is demonstrated (theranostics) [1230]. Therefore, after identification of the target, usually with diagnostic 68Gallium-labelled PSMA, therapeutic radiopharmaceuticals labelled with β(lutetium-177 or yttrium-90) or α(actinium-225)-emitting isotopes could be used to treat metastatic PCa.

The PSMA therapeutic radiopharmaceutical supported by the most robust data is ^{177}Lu-PSMA-617. The first patient was treated in 2014 and early clinical studies evaluating the safety and efficacy of ^{177}Lu-PSMA therapy have demonstrated promising results, despite the fact that a significant proportion of men had already

progressed on multiple therapies [1231]. The early data were based on single-centre experience [1232]. Data from uncontrolled prospective phase II trials reported high response rates with low toxic effects [1233, 1234]. Positive signals are also coming from a randomised pase II trial (TheraP) [1235].

In TheraPpatients for whom cabazitaxel was considered the next appropriate standard treatment after docetaxel and who were highly selected by ^{68}Ga-PSMA-11 and ^{18}FDG PET-CT scans, were randomised to receive ^{177}Lu-PSMA-617 (6.0–8.5 GBq intravenously, every six weeks, for up to six cycles) or cabazitaxel (20 mg/m^2 for up to ten cycles). The primary endpoint was a reduction of at least 50% in PSA. The first endpoint was met (66% vs. 37% for ^{177}Lu–PSMA-617 vs. cabazitaxel, respectively, by intention to treat; difference 29% (95% CI: 16–42; p < 0.0001; and 66% vs. 44% by treatment received; difference 23% [9–37]; p = 0.0016) [1235]. At 36 months follow-up, the secondary endpoint OS was similar in those patients randomly assigned to 177Lu-PSMA versus cabazitaxel (19.1 vs. 19.6 months, difference -0.5, 95% CI -3.7 to + 2.7; ^{177}Lu-PSMA vs. cabazitaxel, respectively), HR: 0.97, 95% CI: 0.7-1.4, p=0.99) [1236].

An open-label phase III trial (VISION) compared ^{177}Lutetium Vipivotid tetraxetan (^{177}Lu-PSMA-617 radioligand therapy) with protocol-permitted SOC (i.e., excluded chemotherapy, immunotherapy, radium-223 and investigational drugs) in mCRPC patients, with PSMA expressing metastases on PET/CT, previously treated with at least one ARPI and one (around 53%) or two taxanes. Imaging-based PFS and OS were the alternate primary endpoints. More than 800 patients were randomised. 177Lu-PSMA-617 plus SOC significantly prolonged both imaging-based PFS and OS, as compared with SOC alone (see Table 6.6.3). Grade 3 or above AEs were higher with ^{177}Lu-PSMA-617 than without (52.7% vs. 38.0%), but QoL was not adversely affected. ^{177}Lu–PSMA-617 has shown to be an additional treatment option in this mCRPC population [1237].

A SR and updated meta-analysis, investigated the proportion of patients with any or more than 50% PSA decrease, and OS. The review, including 69 articles and a total of 4,157 patients, showed that patients treated with ^{177}Lu–PSMA 617 had a significantly higher response to therapy compared to controls, based on ≥ 50% PSA decrease (OR = 5.33, 95% CI: 1.24–22.90, p < 0.05). Meta-analysis revealed an OS of 0.26 according to pooled HRs for any PSA decline, which was significant after 177Lu–PSMA-617 therapy (95% CI: 0.18–0.37, p < 0.00001) and an OS of 0.52 for ≥ 50% PSA decrease, also significant after radioligand (RLT) (95% CI: 0.40–0.67, p < 0.00001) [1238].

There is an increasing interest for PSMA-targeted alpha therapy (^{225}Ac-PSMA) due to the ability to deliver potent higher local radiation more selectively to cancer cells than PSMA-targeted beta therapy, while minimising unwanted damage to the surrounding normal tissues. Additionally, the intensive radiation to cancer cells results in more effective DNA strand breakage and reduces the development of treatment resistance. A meta-analysis, including nine studies with 263 patients, investigated the therapeutic effects of ^{225}Ac-PSMA RLT in patients with metastatic CRPC, pre-treated with chemotherapy, ^{177}Lu-PSMA and/or radium-223. The pooled proportions of patients with more than 50% PSA decline and any PSA decline were 60.99% (95% CI: 54.92%– 66.83%) and 83.57% (95% CI: 78.62%–87.77%), respectively. The estimated mean PFS and mean OS were 9.15 months (95% CI: 6.69–11.03 months) and 11.77 months (95% CI: 9.51–13.49 months), respectively. These findings suggests that ^{225}Ac-PSMA RLT may be an effective treatment option for patients with mCRPC [1239]. Despite the encouraging therapeutic response and survival of patients who received ^{225}Ac-PSMA RLT, major AEs like xerostomia and severe haematotoxicity have to be considered as possible reasons for dose reduction or discontinuation of the therapy.

6.7.8.3 PARP inhibitors for mCRPC

So far, two PARP inhibitors as monotherapy, olaparib and rucaparib, are licenced by the FDA (EMA only approved olaparib) and several other PARP inhibitors are under investigation or were approved only in combination with an ARPI (see chapter 6.7.6.6; e.g., talazoparib, niraparib).

A randomised phase III trial (PROfound) compared the PARP inhibitor olaparib to an alternative ARPI in mCRPC with alterations in ≥ 1 of any qualifying gene with a role in HRR and progression on an ARPI. Most patients were heavily pre-treated with 1–2 chemotherapies and up to 2 ARPIs [248, 1162]. Radiographic PFS by blinded independent central review in the *BRCA1/2* or ATM mutated population (Cohort A) was the first endpoint and significantly favoured olaparib (HR: 0.49, 95% CI: 0.38–0.63). The final results for OS demonstrated a significant improvement among men with *BRCA1/2* or ATM mutations (Cohort A) (p = 0.0175; HR: 0.69, 95% CI: 0.50– 0.97). This was not significant in men with any (other) HRR alteration (Cohort B) (HR: 0.96, 95% CI: 0.63–1.49). Of note, patients in the physician's choice of enzalutamide/abiraterone-arm who progressed, 66% (n = 86/131) crossed over to olaparib.

The most common AEs were anaemia (46.1% vs. 15.4%), nausea (41.4% vs. 19.2%), decreased appetite (30.1% vs. 17.7%) and fatigue (26.2% vs. 20.8%) for olaparib vs. enzalutamide/abiraterone. Among patients receiving olaparib 16.4% discontinued treatment secondary to an AEs, compared to 8.5% of patients receiving enzalutamide/abiraterone. Interestingly, 4.3% of patients receiving olaparib had a pulmonary embolism, compared to 0.8% among those receiving enzalutamide/abiraterone, none of which were fatal. There were no reports of myelodysplastic syndrome or acute myeloid leukaemia. This is the first trial to show a benefit for genetic testing and precision medicine in mCRPC.

The olaparib approval by the FDA is for patients with deleterious or suspected deleterious germline- or somatic HRR gene-mutated mCRPC, who have progressed following prior treatment with enzalutamide or abiraterone. The EMA approved olaparib for patients with *BRCA1* and *BRCA2* alterations [1240]. The recommended olaparib dose is 600 mg daily (300 mg taken orally twice daily), with or without food.

Rucaparib has been approved by the FDA for patients with deleterious BRCA mutations (germline and/or somatic) who have been treated with ARPI and a taxane-based chemotherapy [1241]. Approval was based on the results of the single-arm TRITON2 trial (NCT02952534). The confirmed ORR per independent radiology review in 62 patients with deleterious BRCA mutations was 43.5% (95% CI: 31–57) [1242]. Rucaparib second line after ARPI was studied in the TRITON 3 trial and is discussed in chapter 6.7.7.5

The combination of ARPI plus a PARP inhibitor in first-line mCRPC was studied in several RCTs including AAP plus Olaparib [1193], AAP plus Niraparib [1198] and Enzalutamide plus Talazoparib [1202]. See Table 6.7.2.

6.7.8.4 Sequencing treatment

6.7.8.4.1 ARPI -> ARPI (chemotherapy-naïve mCRPC patients)

The use of sequential ARPIs in mCRPC showed limited benefit in retrospective series as well as in one prospective trial [1245-1252]. In particular in patients who had a short response to the first ARPI for mCRPC (< twelve months), this sequence should be avoided because of known cross resistance and the availability of chemotherapy and PARP inhibitors (if a relevant mutation is present).

In highly selected patients treated for more than 24 weeks with AAP, the sequence with enzalutamide showed some activity with a median rPFS of 8.1 months (95% CI: 6.1–8.3) and an unconfirmed PSA response rate of 27% [1253]. In case the patient is unfit for chemotherapy and a PARP inhibitor, best supportive care should be considered in case no other appropriate treatment option is available (clinical trial or immunotherapy if MSI-high). An ARPI-ARPI sequence should never be the preferred option but might be considered in such patients if the PS still allows for active treatment and the potential side effects seem manageable.

First prospective cross-over data on an ARPI-ARPI sequence [1245] and a SR and meta-analysis suggest that for the endpoints PFS and PSA PFS, but not for OS, abiraterone followed by enzalutamide is the preferred choice [1254].

6.7.8.4.2 ARPI -> PARP inhibitor

This sequence in patients with deleterious or suspected deleterious germline or somatic HRR gene-mutated mCRPC is supported by data from the randomised phase III PROfound trial studying olaparib [1162] and TRITON 3 studying rucaparib [1219]. A subgroup of patients in pROfound was pre-treated with one or two ARPIs and no chemotherapy (35%).

The ARPI-PARP inhibitor sequence versus ARPI-ARPI or ARPI-docetaxel in patients with BRCA 1/ 2 (and ATM) altered tumours was studied in TRITON-3 and showed a significant rPFS benefit in favour of the PARP inhibitor following the first ARPI. These data underscore the importance of early genomic testing in mCRPC patients. (see also chapter 6.7.7.5)

6.7.8.4.3 Docetaxel for mHSPC -> docetaxel rechallenge

There is limited evidence for second- or third-line use of docetaxel after treatment with docetaxel for mHSPC. Docetaxel seems to be less active than ARPI at progression to mCRPC following docetaxel for mHSPC [1255].

6.7.8.4.4 ARPI -> docetaxel or docetaxel -> ARPI followed by PARP inhibitor

Both olaparib and rucaparib are active in biomarker-selected mCRPC patients after ARPI and docetaxel in either sequence [1162, 1241].

6.7.8.4.5 ARPI before or after docetaxel

There is level 1 evidence for both sequences (see Table 6.7.3).

6.7.8.4.6 ARPI –> docetaxel -> cabazitaxel or docetaxel –> ARPI -> cabazitaxel

Both third-line treatment sequences are supported by level 1 evidence. Of note, there is high-level evidence favouring cabazitaxel vs. a second ARPI after docetaxel and one ARPI in particular in patients progressing ≤ twelve months on a prior ARPI. CARD is the first prospective randomised phase III trial addressing this question (see Table 6.7.3) [1164].

Table 6.7.3: Randomised controlled phase II/III - second-line/third-line trials in mCRPC

Study	Intervention	Comparison	Selection criteria	Main outcomes
ABIRATERONE				
COU-AA-301 2012 [1213]	abiraterone + prednisone HR	placebo + prednisone	- Previous docetaxel. - ECOG 0–2. - PSA or radiographic progression.	**OS: 15.8 vs. 11.2 mo.** (p < 0.0001, HR: 0.74, 95% CI: 0.64–0.86; p < 0.0001). FU: 20.2 mo. **rPFS: no change**
COU-AA-301 2011 [1212]				**OS: 14.8 vs. 10.9 mo.** (p < 0.001 HR: 0.65; 95% CI: 0.54–0.77). FU: 12.8 mo. **rPFS: 5.6 vs. 3.6 mo.**
Radium-223				
ALSYMPCA 2013 [1256]	radium-223	placebo	- Previous or no previous docetaxel. - ECOG 0–2. - Two or more symptomatic bone metastases. - No visceral metastases.	**OS: 14.9 vs. 11.3 mo.** (p = 0.002, HR: 0.61; 95% CI: 0.46–0.81). All secondary endpoints show a benefit over best SOC.
CABAZITAXEL				
TROPIC 2013 [1208]	cabazitaxel + prednisone	mitoxantrone + prednisone	- Previous docetaxel. - ECOG 0–2.	**OS: 318/378 vs. 346/377 events** (OR: 2.11; 95% CI: 1.33–3.33). FU: 25.5 months OS ≥ 2 yr 27% vs. 16% PFS: -
TROPIC 2010 [1204]				**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)
CARD 2019 [1164]	cabazitaxel (25 mg/m^2 Q3W) + prednisone + G-CSF	ARTA: abiraterone + prednisone OR enzalutamide	- Previous docetaxel. - Progression ≤ 12 mo. on prior alternative ARPI (either before or after docetaxel)	**OS: 13.6 vs. 11.0 mo.** (p = 0.008, HR: 0.64, 95% CI: 0.46–0.89). **rPFS 8.0 vs. 3.7 mo.** (p < 0.001, HR: 0.54, 95% CI: 0.40–0.73). FU: 9.2 mo.
ENZALUTAMIDE				
AFFIRM 2012 [1214]	enzalutamide	placebo	- Previous docetaxel. - ECOG 0–2.	**OS: 18.4 vs. 13.6 mo.** (p < 0.001, HR: 0.63; 95% CI: 0.53–0.75). FU: 14.4 mo. **rPFS: 8.3 vs. 2.9 mo.** (HR: 0.40; 95% CI: 0.35–0.47, p < 0.0001).

PARP inhibitor				
PROfound 2020 [248, 1162, 1224]	olaparib	abiraterone + prednisolone or enzalutamide; cross-over allowed at progression	- Previous ARPI, - alterations in HRR genes	**rPFS: 7.39 vs. 3.55 mo.** (p < 0.0001, HR: 0.34; 95% CI: 0.25–0.47), conf. ORR 33.3% vs. 2.3% (OR 20.86, 95% CI: 4.18–379.18). **OS: 19.1 mo vs. 14.7 mo.** (in pts with *BRCA1/2*, *ATM* alterations) (p = 0.0175; HR 0.69, 95% CI: 0.5–0.97).
TRITON-3 [1219]	rucaparib (600 mg BID)	docetaxel or abiraterone acetate or enzalutamide	- EOCG 0-1 - Previous one ARPI - BRCA 1/ 2 or ATM alteration	**rPFS: ITT** **10.2 mo vs. 6.4 mo,** HR 0.61; 95% CI, 0.47 to 0.80; (P<0.001 for both comparisons)
Radioligand therapy				
VISION 2021 [1237]	^{177}Lu-PSMA-617 SOC	SOC alone	- Previous at least 1 ARPI and one or two taxane regimens; - Mandatory: PSMA-positive gallium-68 (^{68}Ga)–labelled PSMA-PET scan	**Imaging-based PFS: 8.7 vs. 3.4 mo.** (p < 0.001; HR 0.40; 99.2% CI: 0.29–0.57) **OS: 15.3 vs. 11.3 mo.** (p < 0.001; HR 0.62; 95% CI: 0.5–0.74)
TheraP 2021 [1235, 1236]	^{177}Lu-PSMA-617 (8.5 GBq i.v.q 6-weekly, decreasing 0.5 GBq/cycle; up to 6 cycles)	cabazitaxel (20 mg/m^2 i.v.q 3-weekly, up to 10 cycles)	- Post docetaxel, - Suitable for cabaziaxel	**First endpoint PSA reduction of > 50%:** 66 vs. 37 PSA responses; 66% vs. 37% by ITT; difference 29% (95% CI: 16–42; p < 0.0001; and 66% vs. 44% by treatment received; difference 23% [9–37]; p = 0.0016). **Secondary endpoint OS:** 19.1 vs. 19.6 mo (^{177}Lu-PSMA vs. cabazitaxel). HR: 0.97, 95% CI: 0.7-1.4 (p=0.99)

**Only studies reporting survival outcomes as primary endpoints have been included.*
ARPI = androgen receptor pathway inhibitor; CI = confidence interval; ECOG = Eastern Cooperative Oncology Group; FU = follow-up; GBq = gigabecquerel; HR = hazard ratio; Lu = lutetium; mo = months OS = overall survival; OR = odds ratio; ORR = objective response rate; PSA = prostate-specific antigen; PSMA = prostatespecific membrane antigen; (r)PFS = (radiographic) progression-free survival; SOC = standard of care; yr = year; HRR= homologous recombination repair.

6.7.8.5 Platinum chemotherapy

Cisplatin or carboplatin as monotherapy or combinations have shown limited activity in unselected patients in the pre-docetaxel era [1257]. The combination of cabazitaxel and carboplatin was evaluated in pre-treated mCRPC patients in a randomised phase I/II trial. The combination improved the median PFS from 4.5 months (95% CI: 3.5–5.7) to 7.3 months (95% CI: 5.5–8.2; HR: 0.69, 95% CI: 0.50–0.95, p = 0.018) and the combination was well tolerated [1258]. On a histopathological and molecular level, there is preliminary evidence that platinum adds efficacy in patients with aggressive variant PCa molecular signatures including TP53, RB1, and PTEN [1259].

Patients with mCRPC and alterations in DDR genes are more sensitive to platinum chemotherapy than unselected patients [1260], also after progression on PARP inhibitors. Interestingly, in contemporary retrospective series, unselected patients as well as patients without DDR gene alterations also showed a 50% PSA decline when treated with platinum in up to 36% of patients. In view of the excellent tolerability of e.g., carboplatin monotherapy, platinum could be offered to patients with far advanced mCRPC harbouring DDR gene aberrations after having progressed on standard treatment options. Prospective controlled trials are ongoing.

6.7.9 ***Monitoring of treatment***

Baseline examinations should include a medical history, clinical examination as well as baseline blood tests (PSA, total testosterone level, full blood count, renal function, baseline liver function tests, alkaline phosphatase), bone scan and CT of chest, abdomen and pelvis [1261, 1262]. The use of choline or PSMA PET/CT scans for progressing CRPC is unclear and most likely not as beneficial as for patients with BCR or hormone-naive disease. Flares, PSMA upregulation and discordant results compared with PSA response or progression on ARPI have been described [1263]. Prostate-specific antigen alone is not reliable enough [1264] for monitoring disease activity in advanced CRPC since visceral metastases may develop in men without rising PSA [1265]. Instead, the PCWG2 recommends a combination of bone scintigraphy and CT scans, PSA measurements and clinical benefit in assessing men with CRPC [1266]. A majority of experts at the 2015 Advanced Prostate Cancer Consensus Conference (APCCC) suggested regular review and repeating blood profile every two to three months with bone scintigraphy and CT scans at least every six months, even in the absence of a clinical indication [1261]. This reflects that the agents with a proven OS benefit all have potential toxicity and considerable cost and patients with no objective benefit should have their treatment modified. The APCCC participants stressed that such treatments should not be stopped for PSA progression alone. Instead, at least two of the three criteria (PSA progression, radiographic progression and clinical deterioration) should be fulfilled to stop treatment. For trial purposes, the updated PCWG3 put more weight on the importance of documenting progression in existing lesions and introduced the concept of no longer 'clinically benefiting' to underscore the distinction between first evidence of progression and the clinical need to terminate or change treatment [1267]. These recommendations also seem valid for clinical practice outside trials.

6.7.10 ***When to change treatment***

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. Preferably, any treatment change should precede development of *de novo* symptoms or worsening of existing symptoms. Although, the number of effective treatments is increasing, head-to-head comparisons are still rare, as are prospective data assessing the sequencing of available agents. Therefore it is not clear how to select the most appropriate 'second-line' treatment, in particular in patients without HRR alterations or other biomarkers. A positive example, however, is the CARD trial which clearly established cabazitaxel as the better third-line treatment in docetaxel pre-treated patients after one ARPI compared to the use of a second ARPI [1164].

The ECOG PS has been used to stratify patients. Generally men with a PS of 0–1 are likely to tolerate treatments and those with a PS of > 2 are less likely to benefit. However, it is important that treatment decisions are individualised, in particular when symptoms related to disease progression are impacting on PS. In such cases, a trial of active life-prolonging agents to establish if a given treatment will improve the PS may be appropriate. Sequencing of treatment is discussed in the summary papers published following the 2019 and 2022 APCCC Conferences [1268, 1269].

6.7.11 ***Symptomatic management in metastatic castration-resistant prostate cancer***

Castration-resistant PCa is usually a debilitating disease often affecting the elderly male. A multidisciplinary approach is required with input from urologists, medical oncologists, radiation oncologists, nurses, psychologists and social workers [1268, 1270]. Critical issues of palliation must be addressed when considering additional systemic treatment, including management of pain, constipation, anorexia, nausea, fatigue and depression.

6.7.11.1 Common complications due to bone metastases

Most patients with CRPC have painful bone metastases. External beam RT is highly effective, even as a single fraction [1271, 1272]. A single infusion of a third generation bisphosphonate could be considered when RT is not available [1273]. Common complications due to bone metastases include vertebral collapse or deformity, pathological fractures and spinal cord compression. Cementation can be an effective treatment for painful spinal fracture whatever its origin, clearly improving both pain and QoL [1274]. It is important to offer standard palliative surgery, which can be effective for managing osteoblastic metastases [1275, 1276]. 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 or orthopaedic surgeon consultation should be planned to discuss a possible decompression, followed by EBRT [1277]. Otherwise, EBRT with, or without, systemic therapy, is the treatment of choice.

6.7.11.2 Preventing skeletal-related events

6.7.11.2.1 Bisphosphonates

Zoledronic acid has been evaluated in mCRPC to reduce skeletal-related events (SRE). This study was conducted when no active anti-cancer treatments, but for docetaxel, were available. Six hundred and forty three patients who had CRPC with bone metastases were randomised to receive zoledronic acid, 4 or 8 mg every three weeks for fiveteen consecutive months, or placebo [1278]. The 8 mg dose was poorly tolerated and reduced to 4 mg but did not show a significant benefit. However, at fiveteen and 24 months of follow-up, patients treated with 4 mg zoledronic acid had fewer SREs compared to the placebo group (44 vs. 33%, p = 0.021) and in particular fewer pathological fractures (13.1 vs. 22.1%, p = 0.015). Furthermore, the time to first SRE was longer in the zoledronic acid group. No survival benefit has been seen in any prospective trial with bisphosphonates.

6.7.11.2.2 RANK ligand inhibitors

Denosumab is a fully human monoclonal antibody directed against RANKL (receptor activator of nuclear factor κ-B ligand), a key mediator of osteoclast formation, function, and survival. In M0 CRPC, denosumab has been associated with increased bone-MFS compared to placebo (median benefit: 4.2 months, HR: 0.85, p = 0.028) [1271]. This benefit did not translate into a survival difference (43.9 compared to 44.8 months, respectively) and neither the FDA or the EMA have approved denosumab for this indication [1279].

The efficacy and safety of denosumab (n = 950) compared with zoledronic acid (n = 951) in patients with mCRPC 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 and bone-specific alkaline phosphatase 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 *post-hoc* re-evaluation of endpoints, denosumab showed identical results when comparing SREs and symptomatic skeletal events [1280].

The potential toxicity (e.g., osteonecrosis of the jaw, hypocalcaemia) of these drugs must always be kept in mind (5–8.2% in M0 CRPC and mCRPC, respectively) [1281, 1282]. Patients should have a dental examination before starting therapy as the risk of jaw necrosis is increased by several risk factors including a history of trauma, dental surgery or dental infection [1283]. Also, the risk for osteonecrosis of the jaw increased numerically with the duration of use in a pivotal trial [1284] (one year vs. two years with denosumab), but this was not statistically significant when compared to zoledronic acid [1279]. According to the EMA, hypocalcaemia is a concern in patients treated with denosumab and zoledronic acid. Hypocalcaemia must be avoided by adequate intake of calcium and vitamin D before initiating therapy [1285]. Hypocalcaemia should be identified and prevented during treatment with bone protective agents (risk of severe hypocalcaemia is 8% and 5% for denosumab and zoledronic acid, respectively) [1282]. Serum calcium should be measured in patients starting therapy and monitored during treatment, especially during the first weeks and in patients with risk factors for hypocalcaemia or on other medication affecting serum calcium. Daily calcium (> 500 mg) and vitamin D (> 400 IU equivalent) are recommended in all patients, unless in case of hypercalcaemia [1282, 1286, 1287].

*6.7.12 **Summary of evidence and guidelines for life-prolonging treatments of castrate-resistant***

Summary of evidence	**LE**
Treatment for mCRPC will be influenced by which treatments patients have already been exposed to.	4

Recommendations	**Strength rating**
Ensure that testosterone levels are confirmed to be < 50 ng/dL before diagnosing castrate-resistant PCa (CRPC).	Strong
Counsel, manage and treat patients with metastatic CRPC (mCRPC) in a multidisciplinary team.	Strong
Treat patients with mCRPC with life-prolonging agents.	Strong
Offer mCRPC patients somatic and/or germline molecular testing as well as testing for mismatch repair deficiencies or microsatellite instability.	Strong

6.7.13 *Guidelines for systematic treatments of castrate-resistant disease*

Summary statement for mCRPC first line combination therapy:
The combination of ARPI plus PARP inhibitors showed a significant rPFS benefit in RCTs for unselected patients. However, this benefit is mainly driven by HRR- and even more pronounced by BRCA 1/2- altered patients. So far, no clear OS benefit was seen, and the side effects of PARP inhibitors add substantial toxicity to ARPI monotherapy. Therefore, no recommendation is given for patients without HRR or BRCA 1/2 -mutations and the data will be re-evaluated after longer follow-up.

Recommendations	Strength rating
Base the choice of treatment on the performance status (PS), symptoms, comorbidities, location and extent of disease, genomic profile, patient preference, and on previous treatment for hormone-sensitive metastatic PCa (mHSPC) (alphabetical order: abiraterone, cabazitaxel, docetaxel, enzalutamide, ^{177}lutetium-PSMA-617-radioligand therapy, radium-223, sipuleucel-T, and for patients with DNA homologous recombination repair (HRR) alterations olaparib, olaparib/abiraterone, niraparib/abiraterone, rucaparib, talazoparib/enzalutamide).	Strong
Avoid sequencing of androgen receptor targeted agents.	Weak
Offer chemotherapy to patients previously treated with abiraterone or enzalutamide.	Strong
Offer patients with metastatic castrate-resistant PCa (mCRPC) who are candidates for cytotoxic therapy and are chemotherapy naiive docetaxel with 75 mg/m^2 every three weeks.	Strong
Offer patients previously untreated for mCRPC and harbouring an HRR or BRCA mutation abiraterone in combination with olaparib if the patient is fit for both agents.	Strong
Offer patients previously untreated for mCRPC and harbouring a BRCA mutation abiraterone in combination with niraparib if the patient is fit for both agents.	Strong
Offer patients previously untreated for mCRPC and harbouring an HRR-mutation enzalutamide in combination with talazoparib if the patient is fit for both agents.	Strong
Offer poly(ADP-ribose) polymerase (PARP) inhibitors to pre-treated mCRPC patients with relevant DNA repair gene mutations.	Strong
Offer patients with mCRPC and progression following docetaxel chemotherapy further life-prolonging treatment options, which include abiraterone, cabazitaxel, enzalutamide, radium-223 and olaparib in case of DNA homologous recombination repair (HRR) alterations.	Strong
Base further treatment decisions of mCRPC on PS, previous treatments, symptoms, comorbidities, genomic profile, extent of disease and patient preference.	Strong
Offer abiraterone or enzalutamide to patients previously treated with one or two lines of chemotherapy.	Strong
Offer cabazitaxel to patients previously treated with docetaxel.	Strong
Offer cabazitaxel to patients previously treated with docetaxel and progressing within twelve months of treatment with abiraterone or enzalutamide.	Strong
Offer ^{177}Lu-PSMA-617 to pre-treated mCRPC patients with one or more metastatic lesions, highly expressing PSMA (exceeding the uptake in the liver) on the diagnostic radiolabelled PSMA PET/CT scan.	Strong

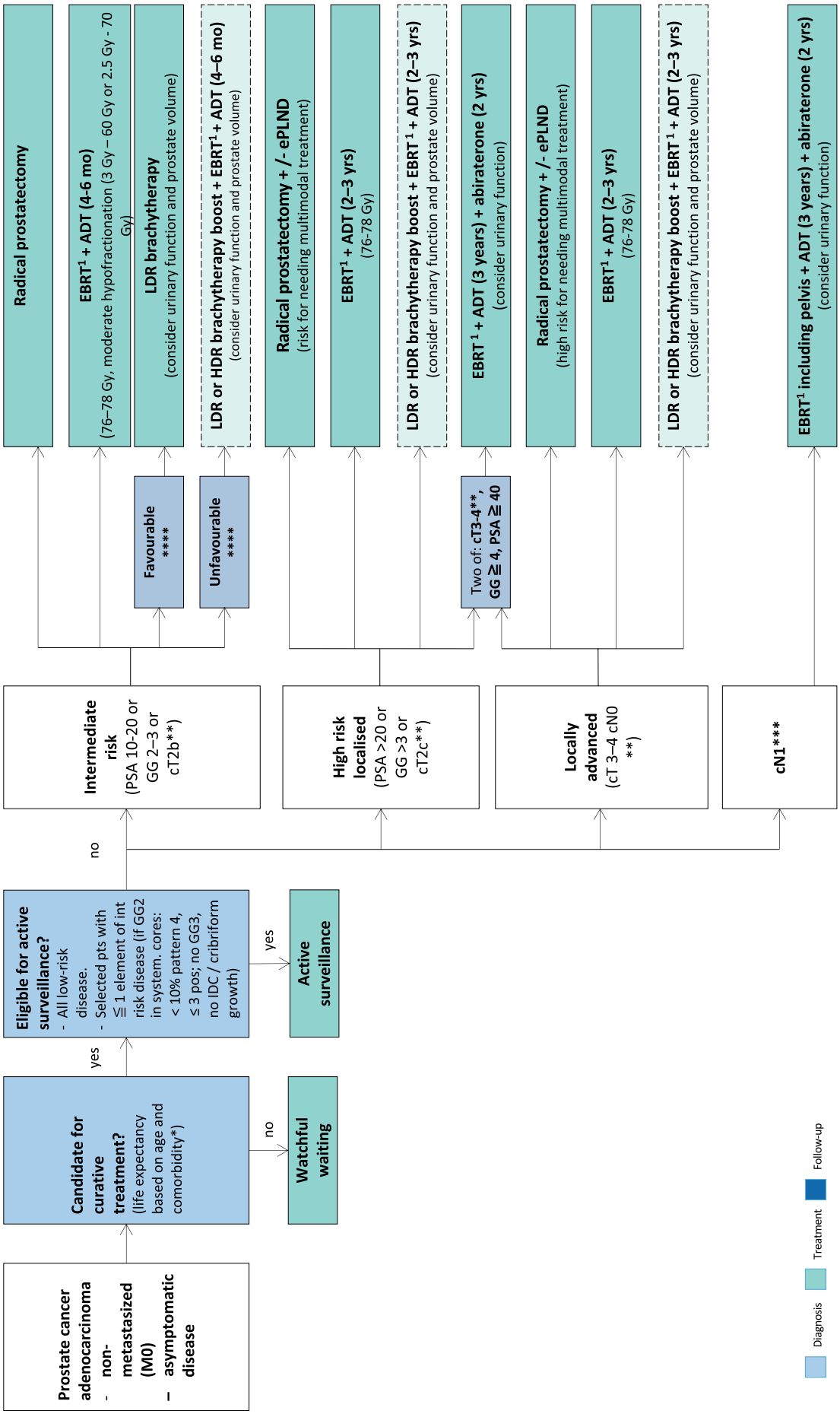
6.7.14 *Guideline for non-metastatic castrate-resistant disease*

Recommendation	Strength rating
Offer apalutamide, darolutamide or enzalutamide to patients with M0 CRPC and a high risk of developing metastasis (PSA-DT < ten months) to prolong time to metastases and overall survival.	Strong

6.7.15 *Guidelines for supportive care of castrate-resistant disease*
These recommendations are in addition to appropriate systemic therapy.

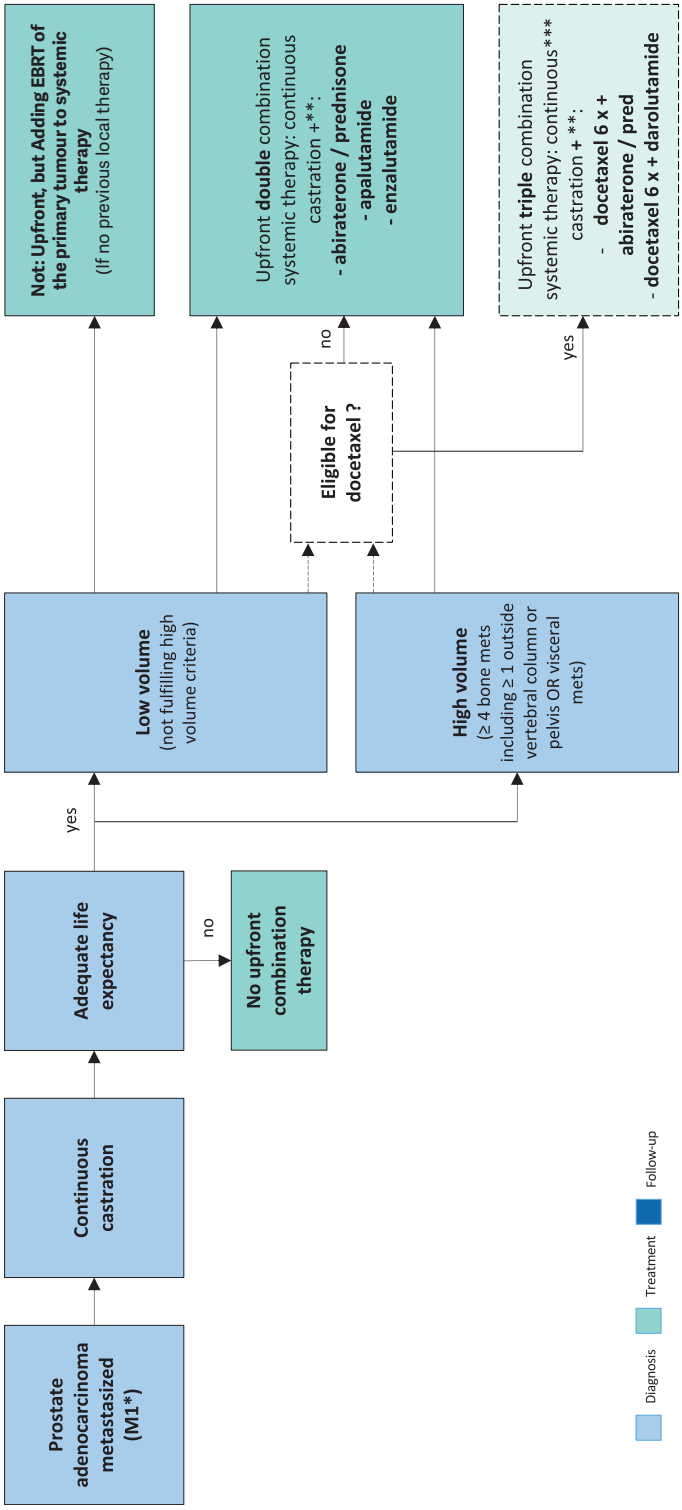
Recommendations	Strength rating
Offer bone protective agents to patients with metastatic prostate cancer and skeletal metastases to prevent osseous complications.	Strong
Monitor serum calcium and offer calcium and vitamin D supplementation when prescribing either denosumab or bisphosphonates.	Strong
Treat painful bone metastases early on with palliative measures such as intensity-modulated radiation therapy/volumetric arc radiation therapy plus image-guided radiation therapy and adequate use of analgesics.	Strong
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.	Strong

Figure 6.4: Treatment non-metastasized (M0) – asymptomatic disease



** Rule of thumb: Life expectancy ten years.*
*** Recommendation based on clinical staging using digital rectal examination, not imaging.*
**** Recommendation based on staging using combination of bone scan and CT.*
***** See text, dependent on GG and (biopsy) volume.*
1EBRT: IMRT/VMAT + IGRT of the prostate.
= weak recommendation.
ADT = androgen deprivation therapy; EBRT =external beam radiotherapy; ECE = extracapsular extension; ePLND = extended pelvic lymph node dissection; GG = grade group; HDR = high-dose rate; IDC = intraducal carcinoma; IGRT = image-guided radiotherapy; IMRT = intensity-modulated radiotherapy; LDR = low-dose rate; VMAT = volumetric modulated arc therapy.

Figure 6.5: Treatment of metastasized (M1*) – disease, M+HSPC



* Based on staging using combination of bone scan and CT.
** Alphabetical order.
***not for low volume, metachronous disease.
1EBRT: IMRT/VMAT + IGRT of the prostate (equivalent of up to 72 Gy in 2 Gy fractions).
= weak recommendation.
EBRT = external beam radiotherapy; IGRT = image-guided radiotherapy; IMRT = intensity-modulated radiotherapy.
#Note: Please be aware that the various options in the following flowcharts present a generalised approach only, and cannot take the management of individual patients into account, nor the availability of resources.

7. FOLLOW-UP

The rationale for following up patients is to assess immediate- and long-term oncological results, ensure treatment compliance and allow initiation of further therapy, when appropriate. In addition, follow-up allows monitoring of side effects or complications of therapy, functional outcomes and an opportunity to provide psychological support to PCa survivors, all of which is covered in Chapter 8.

For patients the most critical aspect of PCa is the diagnosis, the ensuing treatment and follow-up. These must be discussed between the patient and the clinician for shared-decision on the treatment and the planned follow-up, including modalities, periodicity and how this will be communicated to the patient. The patient must be prepared for different potential outcomes of the follow-up, e.g., PSA levels, and what to expect from these. Otherwise, even a very small increase in PSA levels can cause unnecessary fear, even panic.

7.1 Watchful waiting

Watchful waiting refers to conservative management for patients deemed unsuitable for curative treatment from the outset, and patients are clinically 'watched' for the development of local or systemic progression with (imminent) disease-related complaints, at which stage they are then treated palliatively according to their symptoms in order to maintain QoL. (see 6.2.1.)

7.2 Active surveillance strategy

Patients included in an AS programme should be monitored according to the recommendations presented in Section 6.3.1

7.3 Follow-up: After local treatment with curative intent

*7.3.1 **Definition***

Local treatment is defined as RP or RT, either by IMRT plus IGRT or LDR- or HDR-BT, or any combination of these, including neoadjuvant and adjuvant hormonal therapy. Unestablished alternative treatments such as HIFU, cryosurgery and focal therapy options do follow the general principles as presented in this section. In general, a confirmed rising PSA is considered a sign of disease recurrence.

*7.3.2 **Why follow-up?***

The first post-treatment clinic visit focuses on detecting treatment-related complications and assist patients in coping with their new situation apart from providing information on the pathological analysis. Men with PCa are at increased risk of depression and attention for mental health status is required [1288, 1289]. Tumour or patient characteristics may prompt changing the follow-up schedule. Follow-up also allows the introduction of additional / salvage treatments should that be considered necessary in light of the expected life-expectancy, patients symptoms and EAU risk categories for biochemical recurrence (See 6.1 And Table 4.3)

*7.3.3 **How to follow-up?***

The procedures indicated at follow-up visits vary according to the clinical situation. A disease-specific history is mandatory at every follow-up visit and includes psychological aspects, signs of disease progression, and treatment-related complications. Evaluation of treatment-related complications in the post-treatment period is highlighted in Sections 8.2. The examinations used for cancer-related follow-up after curative surgery or RT are discussed below.

7.3.3.1 Prostate-specific antigen monitoring

Measurement of PSA is the cornerstone of follow-up after local treatment. While PSA thresholds depend on the local treatment used, PSA recurrence almost always precedes clinical recurrence [896, 1290]. The key question is to establish when a PSA rise is clinically significant since not all PSA increases have the same clinical value

(see Section 6.4.2) [898]. No prospective studies are available on the optimal timing for PSA testing and the impact on oncological outcomes.

7.3.3.1.1 Prostate-specific antigen monitoring after radical prostatectomy

Following RP, the PSA level is expected to be undetectable. Biochemical recurrence is any rising PSA after prostatectomy as defined in Section 6.3. Prostate-specific antigen level is expected to be undetectable two months after a RP [1291]. Prostate-specific antigen is generally determined every six months until three years and yearly thereafter but the evidence for a specific interval is low [489] and mainly based on the observation that early recurrences are more likely to be associated with more rapid progression [898, 1292, 1293]. A rising PSA may occur after longer intervals up to 20 years after treatment and depends on the initial risk group [820]. A yearly PSA after three years is considered adequate considering the fact that a longer interval to BCR is correlated with a lower EAU-BCR risk score but around 50% of recurrence should be expected beyond three years, follow-up should be terminated if life expectancy drops < 10 years. As mentioned in Section 6.4.2 no definitive threshold can be given for relapse after RP. Persistently measurable PSA in patients treated with RP is discussed in Section 6.3.6.

Ultrasensitive PSA assays remain controversial for routine follow-up after RP. Men with a PSA nadir < 0.01 ng/mL have a high (96%) likelihood of remaining relapse-free within two years [1294]. In addition, post-RP PSA levels > 0.01 ng/mL in combination with clinical characteristics such as ISUP grade group and surgical margin status may predict PSA progression and can be useful to establish follow-up intervals [1293]. However, up to 86% of men were reported to have PSA values below 0.2 ng/mL at five years after an initial PSA nadir below 0.1 ng/mL within six months after surgery [1295].

7.3.3.1.2 Prostate-specific antigen monitoring after radiotherapy

Following RT, PSA drops more slowly as compared to post RP. A PSA nadir < 0.5 ng/mL is associated with a favourable outcome after RT although the optimal cut-off value remains controversial [1296]. The interval before reaching the PSA nadir can be up to three years, or more. At the 2006 RTOG-ASTRO Consensus Conference the Phoenix definition of radiation failure was proposed to establish a better correlation between definition and clinical outcome (mainly metastases), namely, an increase of 2 ng/mL above the post-treatment PSA nadir [897]. This definition also applies to patients who received ADT [897].

7.3.3.2 Digital rectal examination

Local recurrence after curative treatment is possible without a concomitant rise in PSA level although very rarely [1297]. This has only been proven in patients with unfavourable undifferentiated tumours. Prostate specific antigen and DRE comprise the most useful combination for first-line examination in follow-up after RT but the role of DRE was questioned since it failed to detect any local recurrence in the absence of a rising PSA in a series of 899 patients [1298]. In a series of 1,118 prostatectomy patients, no local histologically proven recurrence was found by DRE alone and PSA measurement may be the most efficient test needed after RP [1299, 1300].

7.3.3.3 Transrectal ultrasound, bone scintigraphy, CT, MRI and PET/CT

Imaging techniques have no place in routine follow-up of localised PCa as long as the PSA is not rising. Imaging is only justified in patients for whom the findings will affect treatment decisions, either in case of BCR or in patients with symptoms (see Section 6.4.4.3 for a more detailed discussion).

7.3.3.4 Functional follow-up

All local treatments for PCa may cause short- and long-term side effect of various degree that will affect the patients' QoL. For quality control, and in order to help the patient in choosing the optimal treatment for him, it is essential that the functional outcomes of any treatment given is measured and registered by validated and reproducable methods. In order to adress side effects and their impact of QoL specific tools or 'patient-reported outcome measures' (PROMs) have been developed and validated for men with PCa. These questionnaires assess common issues after PCa diagnosis and treatment and generate scores which reflect the impact on perceptions of HRQoL. For further discussion on this see Section 8.3.

7.3.4 ***How long to follow-up?***

Most patients who fail treatment for PCa do so within seven years after local therapy [1243]. Patients should be followed more closely during the initial post-treatment period when risk of failure is highest. PSA measurement, disease-specific history and DRE (if considered) are recommended every six months until three years and then annually. Whether follow-up should be stopped if PSA remains undetectable (after RP) or stable (after RT) remains an unanswered question, but it seems fair that follow-up is only done to the point that if a recurrence is found the patient is fit enough for salvage therapy.

Risk assessment to predict metastases-free and PCa-specific survival after recurrence after primary treatment may guide individual decisions on a need for longer follow-up [825, 898, 1244]. Even in men with a PSA-DT less than ten months after RP who choose to defer treatment, a median MFS of 192 months and OS of 204 months from RP was observed, indicating the relatively long disease-free intervals observed in men with a rising PSA after local treatment [1301].

Symptomatic recurrence without a PSA rise is extremely rare, however, the symptoms typical for recurrent disease may vary and are poorly defined by published data. In case of the following symptoms PSA testing should be performed to exclude a possible cancer recurrence in particular in men not followed up by regular testing of their PSA levels: pelvic/skeletal pain, haematuria, progressive LUTS, progressive lower body oedema, progressive bowel complaints or complaints of fatigue, sarcopenia or unexplained weight loss [1302].

7.3.5 Summary of evidence and guidelines for follow-up after treatment with curative intent

Summary of evidence	LE
A detectable PSA, indicating a relaps of the disease, must be differentiated from a clinically meaningful relapse. The PSA threshold that best predicts further metastases after RP is > 0.4 ng/mL and > NADIR + 2 ng/mL after IMRT/VMAT plus IGRT (± ADT).	3

Recommendations	Strength rating
Routinely follow-up asymptomatic patients by obtaining at least a disease-specific history and a prostate-specific antigen measurement.	Strong
At recurrence, only perform imaging if the result will affect treatment planning.	Strong

7.4 Follow-up: During first line hormonal treatment (androgen sensitive period)

7.4.1 Introduction

Androgen deprivation therapy is used in various situations: combined with RT for localised or locally-advanced disease, as monotherapy for a relapse after a local treatment, or in the presence of metastatic disease often in combination with other treatments. All these situations are based on the benefits of testosterone blockage or suppression either by drugs (LHRH agonists or antagonists) or orchidectomy. Inevitably, the disease will become castrateresistant, although ADT will be maintained.

This section addresses the general principles of follow-up of patients on ADT alone. Section 6.5.3 includes further information on other drug treatments. Furthermore the specific follow-up needed for every single drug is outside the scope of this text, as is follow-up after chemotherapy.

To detect disease- and treatment-related complaints, regular clinical follow-up is mandatory and cannot be replaced by imaging or laboratory tests alone.

7.4.2 Purpose of follow-up

The main objectives of follow-up in patients receiving ADT are to ensure treatment compliance, to monitor treatment response, to detect side effects early, and to guide treatment at the time point of clinical progression. After the initiation of ADT, it is recommended that patients are evaluated every three to six months. This must be individualised and each patient should be advised to contact his physician in the event of troublesome symptoms. This is even more important for patients who receive a combination of ADT and other potent medication, e.g., ARPI where the frequency of follow-up is monthly for the first three months, for their disease.

7.4.3 General follow-up of men on ADT

Patients under ADT require regular follow-up, including monitoring of serum testosterone, creatinine, liver function and metabolic parameters at three to six month intervals. Men on ADT can experience toxicity independent of their disease stage. Androgen deprivation therapy reduces bone density gradually, increasing the risk of fractures [1303]. It is therefore essential to asses bone density before and during treatment with ADT with or without a combination with other drugs.

As the consequenses of ADT are so varying, a structured follow-up including lab results, radiology and QoL, may be of value both for the patient and for the treating physician [1304].

7.4.3.1 Testosterone monitoring

Testosterone monitoring should be considered standard clinical practice in men on ADT. Many men receiving medical castration will achieve a castrate testosterone level (< 20 ng/dL), and most a testosterone level < 50 ng/dL. However, approximately 13–38% of patients fail to achieve these levels and up to 24% of men may experience temporary testosterone surges (testosterone > 50 ng/dL) during long-term treatment [1291] referred

to as 'acute on-chronic effect' or 'breakthrough response' [1305]. Breakthrough rates for the < 20 ng/dL threshold were found to be more frequent (41.3%) and an association with worse clinical outcomes was suggested [1305].

The timing of measurements is not clearly defined. A three to six month testosterone level assessment has been suggested to ensure castration is achieved (especially during medical castration) and maintained. In case a castrate testosterone level is not reached, switching to another agonist or antagonist or to an orchiectomy should be considered. In patients with a confirmed rising PSA and/or clinical progression, serum testosterone must be evaluated in all cases to confirm a castration-resistant state. Ideally, suboptimal testosterone castrate levels should be confirmed with an appropriate assay [1306, 1307]. After ADT cessation (intermittent treatment or temporary ADT use as with EBRT) testosterone recovery is dependent on patients age and the duration of ADT [1308, 1309].

7.4.3.2 Liver function monitoring

Liver function tests will detect treatment toxicity (especially applicable for NSAA), but rarely indicate disease progression. Men on combined ADT should have their transaminase levels checked at least yearly but in particular in the first six months of treatment initiation since liver function disorders were observed relatively early in the majority of patients in larger trials [1310]. In view of potential liver toxicity a more frequent check is needed with some drugs (including abiraterone acetate) [1311]. Alkaline phosphatase may increase secondary to bone metastases and androgen-induced osteoporosis, therefore it may be helpful to determine bone-specific isoenzymes as none are directly influenced by ADT [1312].

7.4.3.3 Serum creatinine and haematological parameters

Estimated glomerular filtration rate monitoring is good clinical practice as an increase may be linked to ureteral obstruction or bladder retention. A decline in haemoglobin is a known side effect of ADT. A significant decline after three months of ADT is independently associated with shorter progression-free and OS rates and might explain significant fatigue although other causes should be considered [1313]. Anaemia is often multi-factorial and other possible aetiologies should be excluded. An early decrease in haemoglobin three months after ADT initiation predicted better survival whereas a decrease beyond six months was associated with poor outcome in the SPCG-5 population [1314]. Radiotherapy to more extensive bone metastases locations may result in myelosuppression and haematological toxicity [1315, 1316].

7.4.3.4 Monitoring of metabolic complications

The most severe complications of androgen suppression are metabolic syndrome, cardiovascular morbidity, mental health problems, and bone resorption (see Section 8.2.5).

All patients should be screened for diabetes by checking fasting glucose and HbA1c (at baseline and routinely) in addition to checking blood lipid levels. Men with impaired glucose tolerance and/or diabetes should be referred for an endocrine consultation. Prior to starting ADT a cardiology consultation should be considered in men with a history of cardiovascular disease and in men older than 65 years. Men on ADT are at increased risk of cardiovascular problems and hypertension and regular checks are required [1317]. More profound androgen ablation resulted in a higher cardiovascular toxicity [1318] and cardio-respiratory fitness decreased even after six months of ADT [1319]. The prematurely closed PRONOUNCE study found no difference at twelve months in major adverse cardiovascular events between men receiving degarelix or leuprolide [1320].

7.4.3.5 Monitoring bone problems

Androgen deprivation therapy increases the risk of osteoporosis. A combination of ADT with apalutamide, darolutamide, enzalutamide, abiraterone plus prednisone or docetaxel increases the fracture risk even more [1123, 1321, 1322]. Administration of ADT for more than a year, as compared to less than one year, showed a higher risk of osteoporosis (HR: 1.77 and 1.38, respectively) [1323]. Several scores (e.g., Fracture Risk Assessment Tool [FRAX score], Osteoporosis Self-Assessment Tool [OST], Osteoporosis Risk Assessment Instrument [ORAI], Osteoporosis Index of Risk [OSIRIS], Osteoporosis Risk Estimation [SCORE]) can help identify men at risk of osteoporotic complications but validation of these scores in the ADT setting is required (see Section 8.3.2.2) [1221, 1324, 1325].

Routine bone monitoring for osteoporosis should be performed at the start of ADT using dual emission X-ray absorptiometry (DEXA) scan [1222, 1326, 1327]. Presence of osteoporosis should prompt the use of bone protective agents. The criteria for initiation of bone protective agents are mentioned in Section 8.3.2.2. If no bone protective agents are given, a DEXA scan should be done regularly, at least every two years [1328].

A review summarising the incidence of bone fractures showed an almost doubling of the risk of fractures when using ADT depending on patients' age and duration and type of ADT with the highest incidence in older men and men on additional novel ARPI medication across the entire spectrum of disease [1329]. In case of an osteoporotic fracture a bone protective agent is mandatory. Vitamin D and calcium levels should be regularly monitored when patients receive ADT and patients should be supplemented if needed (see Section 8.3.2.2).

7.4.3.6 Monitoring lifestyle, cognition, fatigue and sexual function

Lifestyle (e.g., diet, exercise, smoking status, etc.) affects QoL and potentially outcome [1312]. During follow-up men should be counselled on the beneficial effects of exercise to avoid ADT-related toxicity [1330]. Androgen deprivation therapy may affect mental and cognitive health and men on ADT are three times more likely to report depression [1331]. Attention to mental health should therefore be an integral part of the follow-up scheme. Men on ADT may experience complaints of fatigue possibly related to systemic inflammation [1332]. Reduced cognitive performance and fatigue may arise within six months after initiation of ADT but can improve over time [1333]. Another apect of starting ADT is that it leads to sexual dysfunction, causing > 80% of couples to cease sexual activity completely. This aspect affects patients as well as their partners and couple counselling should be considered [1334].

*7.4.4 **Methods of follow-up in men on ADT without metastases***

7.4.4.1 Prostate-specific antigen monitoring

Prostate-specific antigen is a key marker for following the course of androgen-sensitive non-metastasised PCa. Imaging should be considered when PSA is rising > 2 ng/mL or in case of symptoms suggestive of metastasis.

7.4.4.2 Imaging

In general, asymptomatic patients with a stable PSA level do not require further imaging, although care needs to be taken in patients with aggressive variants when PSA levels may not reflect tumour progression [1335]. New bone pain requires at least targeted imaging and potentially a bone scan. When PSA progression suggests CRPC status and treatment modification is considered, imaging, by means of a bone and CT scan, is recommended for restaging. Detection of metastases greatly depends on imaging (see Section 5.8).

*7.4.5 **Methods of follow-up in men under ADT for hormone-sensitive metastatic PCa***

In metastatic patients it is of the utmost importance to counsel about early signs of spinal cord compression, urinary tract complications (ureteral obstruction, bladder outlet obstruction) or bone lesions that are at an increased fracture risk. The intervals for follow-up in M1 patients should be guided by patients' complaints and can vary. Since most men will receive another anti-cancer therapy combined with ADT such as ARPI, chemotherapy ,local RT, or combinations, follow-up frequency should also be dependent on the treatment modality. The specific points related to follow-up during the castrate-resistant situation are detailed in Section 6.7.9.

7.4.5.1 PSA monitoring

In men on ADT alone, a PSA decline to < 4 ng/mL suggests a likely prolonged response and follow-up visits may be scheduled every three to six months provided the patient is asymptomatic or clinically improving. This applied to men on ADT monotherapy as well as after ADT plus docetaxel [1094]. Depending on symptoms and risk assessment, more frequent visits may be indicated. Treatment response may be evaluated based on a change in serum PSA level [1093, 1094] and bone- and CT scan although there is no consensus about how frequently these should be performed [1268]. A rise in PSA level usually precedes the onset of clinical symptoms by several months. A rising PSA should prompt assessment of testosterone level, which is mandatory to define CRPC status, as well as restaging using imaging. However, it is now recognised that a stable PSA during ADT is not enough to characterise a non-progressive situation [1336].

7.4.5.2 Imaging as a marker of response in metastatic PCa

Treatment response in soft-tissue metastases can be assessed by morphological imaging methods using the Response Evaluation Criteria in Solid Tumours (RECIST) criteria. However, these criteria cannot be used in bone where response assessment is difficult [1337, 1338].

When bone scan is used to follow bone metastases, a quantitative estimation of tracer uptake at bone scan can be obtained through automated methods such as the Bone Scan Index [1339]. Nonetheless, bone scan is limited by the so-called 'flare' phenomenon which is defined by the development of new images induced by treatment on a first follow-up scan which, after longer observation, actually represent a favourable response. Flare is observed within eight to twelve weeks of treatment initiation and can lead to a false-positive diagnosis of disease progression. Computed tomography cannot be used to monitor sclerotic bone lesions because bone sclerosis can occur under effective treatment and reflects bone healing. Magnetic resonance imaging

can directly assess the bone marrow and demonstrate progression based on morphologic criteria or changes in apparent diffusion coefficient. A standardisation for reporting is available [1340]. The ability of PET/CT to assess response has been evaluated in a few studies. Until further data are available, MRI and PET/CT should not be used outside trials for treatment monitoring in metastatic patients [1341].
Men with metastasised PCa on ADT should also in the absence of a PSA rise be followed up with regular imaging since twenty-five percent of men with, or without, docetaxel in the CHAARTED trial developed clinical progression without a PSA rise [1336]. One in eight men with a PSA < 2 ng/mL showed clinical progression [1336]. The addition of docetaxel to ADT in the CHAARTED trial population did not reduce the incidence of clinical progression at low PSA values and this rate was similar for both low- and high-volume disease as per CHAARTED criteria [1336]. However, the optimal timing and image modality to be used remain unclear, as is the real clinical value of any findings.

*7.4.6 **Guidelines for follow-up during hormonal treatment***

Recommendations	**Strength rating**
The follow-up strategy must be individualised based on stage of disease, prior symptoms, prognostic factors and the treatment given.	Strong
In patients with stage M0 disease, schedule follow-up at least every six months. As a minimum requirement, include a disease-specific history, serum prostate-specific antigen (PSA) determination, as well as liver and renal function in the diagnostic work-up.	Strong
In M1 patients, schedule follow-up at least every three to six months.	Strong
In patients on long-term androgen deprivation therapy (ADT), measure initial bone mineral density to assess fracture risk.	Strong
In patients receiving combination treatment for offer bone protection to avoid fractures	Strong
During follow-up of patients receiving ADT, check PSA and testosterone levels and monitor patients for symptoms associated with metabolic syndrome as a side effect of ADT.	Strong
In patients on long-term ADT, as a minimum requirement, include a disease-specific history, haemoglobin, serum creatinine, alkaline phosphatase, lipid profiles and HbA1c level measurements.	Strong
Counsel patients (especially with M1b status) about the clinical signs suggestive of spinal cord compression.	Strong
When disease progression is suspected, restaging is needed and the subsequent follow-up adapted/individualised.	Strong
In patients with suspected progression, assess the testosterone level. By definition, castration-resistant PCa requires a testosterone level < 50 ng/dL (< 1.7 nmol/L).	Strong

8. QUALITY OF LIFE OUTCOMES IN PROSTATE CANCER

This chapter is presented in two parts. The first (Section 8.2) will summarise long-term consequences (≥ twelve months) of therapies for PCa. Based on two SRs, the second (Section 8.3) provides evidence-based recommendations for supporting patients when selecting primary treatment options for localised disease and also supportive interventions aimed at improving disease-specific QoL across all stages of disease.

8.1 Introduction

Quality of life and personalised care go hand in hand. Treating PCa can affect an individual both physically and mentally, as well as close relations and work or vocation. These multifaceted issues all have a bearing on an individual's perception of QoL [1342, 1343]. Approaching care from a holistic point of view requires the intervention of a multi-disciplinary team including urologists, medical oncologists, radiation oncologists, oncology nurses, behavioural practitioners and many others including fellow patients. Attention to the psychosocial concerns of people with PCa is integral to quality clinical care, and this can include the needs of carers and partners [1344]. Prostate cancer care should not be reduced to focusing on the organ in isolation: side effects or late adverse effects of treatment can manifest systemically and have a major influence on the patient's QoL. Psychological distress can be caused by the cancer diagnosis itself, cancer symptoms and/or treatment side effects [1345]. Taking QoL into consideration relies on understanding the patient's values and preferences so that optimal treatment proposals can be formulated and discussed. Cross-sectional patient reported outcomes studies in general PCa populations show the impact of treatment on global and disease specific QoL is greater than that described in clinical trial populations who often have less co-morbidity and belong to higher socio-economic groups. Individuals undergoing two or more treatments have more symptoms and greater impact on QoL [1346, 1347]. Subgroups of people including those with poor general health, being unmarried, older age and/or pre-existing depressive symptoms are more at risk of long-term mental health issues following treatment for PCa [1348].

8.2 Adverse effects of PCa therapies

*8.2.1 **Active surveillance***

In a SR [1349] on the long-term (> five year) health-related QoL in patients on active surveillance, it was observed that there were differences in specific functional outcomes between patients on AS and surgery or radiotherapy, ≥ five year after treatment. In patients on AS, the overall HRQoL and psychological well-being outcomes were good. All studies comparing AS with active treatment found no substantial or consistent difference in general HRQoL PROMs between groups. In preservation of continence there is a clear advantage for AS over, active treatment, particularly to RP. Results suggest that even after extended periods, continence is still considerably superior in AS to that in RP. Obstructive voiding symptoms were more common in patients on AS than in post-operative patients. In the domain of sexual function, it is seen that AS group has better than or comparable sexual function to that in the active treatment group. Studies comparing AS with that of PCa-free patients had mixed results with papers observing no statistically significant difference and others reporting that sexual function was, at least numerically, worse in patients on AS than in PCa-free patients. All patients on AS report good quality of life, similar to that in individuals without prostate cancer [1350]. Regarding anxiety it was seen in a registry on active surveillance in the USA that men undergoing active surveillance, had a moderate risk of cancer-specific anxiety that significantly decreases over time. Patients considering active surveillance can be informed that, although it is common experience some anxiety initially, most men rapidly adjust and report low levels of anxiety within two years [1350].

*8.2.2 **Surgery***

A lack of clear consensus in reporting surgical complications following RP, specifically urinary incontinence and stricture rates, and the introduction of different techniques has resulted in a wide variation in the types of complications reported, as well as variation in the overall incidence of complications [1351-1354]. The most common post-operative complication is ED but other related issues to consider include dry ejaculation, which occurs with removal of the prostate, change in the quality of orgasm and occasional pain on orgasm. Men also complain of loss of penile length (3.73%, 19/510 men) [1355]. The second most commonly occurring complication is long-term incontinence [1351-1354] but voiding difficulties may also occur associated with bladder neck contracture (e.g., 1.1% after RALP) [1356].

A key consideration is whether long-term consequences of surgery are reduced by using newer techniques such as RALP. Systematic reviews have documented complication rates after RALP [612-616], and can be compared with contemporaneous reports after RRP [617]. From these reports, the mean continence rates at twelve months were 89–100% for patients treated with RALP and 80–97% for patients treated with

RRP. A prospective controlled non-randomised trial of patients undergoing RP in fourteen centres using RALP or RRP demonstrated that at twelve months after RALP, 21.3% were incontinent, as were 20.2% after RRP. The unadjusted 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 unadjusted OR was 0.81 (95% CI: 0.66–0.98) [618, 1357]. Further follow-up demonstrates similar functional outcomes with both techniques at 24 months [1357, 1358]. A single-centre randomised phase III study comparing RALP and RRP (n = 326) also demonstrates similar functional outcomes with both techniques at 24 months [1359]. Prostatectomy was found to increase the risk of complaints from an inguinal hernia, in particular after an open procedure when compared to minimally-invasive approaches [1360, 1361]. For those undergoing minimally-invasive procedures port site hernia has been reported in 0.66% after inserting 12 mm bladeless trocar and can occur more rarely with 8 mm and 5 mm trocars [1362]. Another complication after primary treatment is lower limb and genital lymphedema. A SR found a prevalence of (0-14%) lower limb and (0-1%) genital lymphedema after radical prostatectomy with PLND [1363] and between 0-9% and 0-8% in patients after irradiation on the LNs. In the subgroup that underwent pelvic irradiation after staging pelvic LNs dissections the prevalence of lower limb (18-29%) and genital (2-22%) is substantially elevated.

*8.2.3 **Radiotherapy***

8.2.3.1 Side effects of external beam radiotherapy

Analysis of the toxicity outcomes of the ProtecT trial shows that patients treated with EBRT and six months of ADT report bowel toxicity including persistent diarrhoea, bowel urgency and/or incontinence and rectal bleeding (described in detail in Section 8.3.1.1 below) [1364]. Participants in the ProtecT study were treated with 3D-CRT and studies using IMRT demonstrate less bowel toxicity than noted previously with 3D-CRT [1365].

A SR and meta-analysis of observational studies comparing patients exposed or unexposed to RT in the course of treatment for PCa demonstrates an increased risk of developing second cancers for bladder (OR: 1.39), colorectal (OR: 1.68) and rectum (OR: 1.62) with similar risks over lag times of five and ten years. Absolute excess risks over ten years are small (1–4%) but should be discussed with younger patients in particular [1366].

Patient-reported outcomes suggest a temporary drop in the EPIC hormonal and sexual domains when six months af ADT was added to radiotherapy, with a disappearance of any clinical relevant difference at one year [1147, 1367].

8.2.3.2 Side effects from brachytherapy

Some patients experience significant urinary complications following implantation such as urinary retention (1.5-22%), with post-implantation TURP reported as being required in up to 8.7% of cases, and incontinence (0–19%) [1368]. Chronic urinary morbidity is more common with combined EBRT and BT and can occur in up to 20% of patients, depending on the severity of the symptoms before BT. Urethral strictures account for at least 50% of urinary complications and can be resolved with dilation in the majority [719, 726]. Prevention of morbidity depends on careful patient selection and IPSS score, backed up by urodynamic studies.

*8.2.4 **Local primary whole-gland treatments other than surgery or radiotherapy***

8.2.4.1 Cryosurgery

In a SR and meta-analysis there was evidence that the rate of urinary incontinence at one year was lower for cryotherapy than for RP, but the size of the difference decreased with longer follow-up [738]. There was no significant difference between cryotherapy vs. EBRT in terms of urinary incontinence at one year (< 1%); cryotherapy had a similar ED rate (range 0–40%) to RP at one year. There were insufficient data to compare cryotherapy vs. EBRT in terms of ED.

8.2.4.2 High-intensity focused ultrasound

In terms of toxicity there are insufficient data on urinary incontinence, ED, or bowel dysfunction to draw any conclusions, although at one-year HIFU had lower incontinence rates than RP (OR: 0.06, 95% CI: 0.01–0.48) [738].

*8.2.5 **Androgen deprivaton therapy***

A summary of psychological impacts due to the use of ADT such as sexual function, mood, depression, cognitive function, and impact on partners can be found in two clinical reviews [1369, 1370].

A small RCT evaluated the QoL at one-year follow-up in patients with PSA only relapse after primary therapy without evidence of metastasis, between various ADT regimens, or no treatment. Patients treated by ADT reported a significant decline in spatial reasoning, spatial abilities and working memory as well as increased depression, tension, anxiety, fatigue, and irritability during treatment [1371]. Conversely, a prospective observational study with follow-up out to three years failed to demonstrate any association with cognitive decline in men on ADT when compared to men with PCa not treated with ADT and healthy controls [1372]. A prospective observational study of locally advanced PCA or BCR after local therapy found that immediate ADT

was associated with a lower overall QoL compared to deferred treatment [1373]. 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 patients undergoing orchiectomy. The stage at diagnosis had no effect on health outcomes [1374].

8.2.5.1 Sexual function

Cessation of sexual activity is very common in people undergoing ADT, affecting up to 93% [1375]. Androgen deprivation therapy reduces both libido and the ability to gain and maintain erections. The management of acquired ED is mostly non-specific [1376].

Using a specific non-validated questionnaire, bicalutamide monotherapy showed a significant advantage over castration in the domains of physical capacity and sexual interest (not sexual function) at twelve months [1377]. 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 [1378], preserved libido and erectile function [1379].

8.2.5.2 Hot flushes

Hot flushes are a common side effect of ADT (prevalence estimated between 44–80% of men on ADT) [1375]. They appear three months after starting ADT, usually persist long-term and have a significant impact on QoL.

Serotonin re-uptake inhibitors (e.g., venlafaxine or sertraline) appear to be effective in men but less than hormone therapies based on a prospective RCT comparing venlafaxine, 75 mg daily, with medroxyprogesterone, 20 mg daily, or cyproterone acetate, 100 mg daily [1380]. After six months of LHRH (n = 919), 311 men had significant hot flushes and were randomised to one of the treatments. Based on median daily hot-flush score, venlafaxine was inferior -47.2% (interquartile range -74.3 to -2.5) compared to -94.5% (-100.0 to -74.5) in the cyproterone group, and -83.7% (-98.9 to -64.3) in the medroxyprogesterone group. Another RCT (n = 78) compared oestradiol (transdermal 0,9mg or 0,1% gel) to placebo. After six months oestradiol reduced daily hot flushes frequency (mean adjusted difference MAD -1,6, p=0.04) but the effect on weekly hot flushes was not significant (MAD -19,6 p=0.11) [1381].

With a placebo effect influencing up to 30% of patients [1382] , the efficacy of clonidine, veralipride, gabapentin [1383] and acupuncture [1384] need to be compared in prospective RCTs.

8.2.5.3 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% RR with long-term ADT) [1385]. Severe fractures in men are associated with a significant risk of death [1386]. A precise evaluation of BMD should be performed by DEXA, ideally 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 and causes should be investigated. Other risk factors include increasing age, BMI of 19 or less, history of previous fracture or parent with fractured hip, current smoking, use of glucocorticoids, rheumatoid arthritis, alcohol consumption > two units per day, history of falls and a number of other chronic medical conditions [1387]. Fracture risk algorithms which combine BMD and clinical risk factors such as FRAX score can be used to guide treatment decisions, but uncertainty exists regarding the optimal intervention threshold, therefore no specific risk algorithm can be recommended for men on ADT for PCa. Obesity (increase in body fat mass by up to 10% and/or BMI > 30) and sarcopenia (decrease in lean tissue mass by up to 3%) as well as weight loss are common and occur during the first year of ADT [1388]. These changes increase the fracture risk [1389]. It is suggested that adding ARTA to ADT will increase this risk. This was also seen in a SR and meta-analysis [1390]. It was found that the use of ARTA was associated with an increase in fractures. Eleven studies were included with a total population of 11,382 men (median [range] age: 72 [43-97] years), with 6,536 in the ARTA group and 4,846 in the control group. Participants in the ARTA group could have received enzalutamide, apalutamide, or darolutamide in combination with androgen deprivation therapy or other enzalutamide combinations; patients in the control group could have received placebo, bicalutamide, or abiraterone. The incidence of fracture was 242 fractures (4%) in the ARTA group and 107 fractures (2%) in the control group. Use of an ARTA was associated with an increased risk of fractures: all-grade fracture (RR, 1.59; 95% CI, 1.35-1.89; p <.001), and likely grade 3 or greater fracture (RR, 1.71; 95% CI, 1.12-2.63; p =.01).

Bicalutamide monotherapy may have less impact on BMD but is limited by its suboptimal efficacy for M1 disease [1391, 1392]. The intermittent LHRH-agonist modality might be associated with less bone impact [1393].

8.2.5.4 Metabolic effects

Lipid alterations are common and may occur as early as the first three months of treatment [1388]. Androgen deprivation therapy also decreases insulin sensitivity and increases fasting plasma insulin levels, which is a marker of insulin resistance. In diabetic patients, metformin appears to be an attractive option for protection against metabolic effects based on retrospective analysis [1394], 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 [1395]:

- waist circumference > 102 cm;
- serum triglyceride > 1.7 mmol/L;
- blood pressure > 130/80 mmHg or use of medication for hypertension;
- high-density lipoprotein (HDL) cholesterol < 1 mmol/L;
- glycaemia > 5.6 mmol/L or the use of medication for hyperglycaemia.

The prevalence of a metabolic-like syndrome is higher during ADT compared with men not receiving ADT [1396]. Skeletal muscle mass heavily influences basal metabolic rate and is in turn heavily influenced by endocrine pathways [1397]. Androgen deprivation therapy-induced hypogonadism results in negative effects on skeletal muscle health. A prospective longitudinal study involving 252 men on ADT for a median of 20.4 months reported lean body mass decreases progressively over three years; 1.0% at one year, 2.1% at two years, and 2.4% at three years which appears more pronounced in men at ≥ 70 years of age [1398].

8.2.5.5 Cardiovascular morbidity

Cardiovascular mortality is a common cause of death in PCa patients [1030, 1399, 1400]. Several studies showed that ADT after only six months was associated with an increased risk of diabetes mellitus, cardiovascular disease, and myocardial infarction [1401]. The RTOG 92-02 [1402] and 94-08 [1403] 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 both a secondary analysis of PLCO trial, even among subgroups with pre-existing cardiovascular disease [1404] and a meta-analysis of trials RTOG 8531, 8610, 9202, EORTC 30891 and EORTC 22863 [1405]. However, serious concerns about the conclusions of this meta-analysis have been raised due to poor consideration of bias in the included studies [1406, 1407]. A meta-analysis of observational data reports consistent links between ADT and the risk of cardiovascular disease patients treated for PCa, e.g., the associations between LHRH agonists and non-fatal or fatal myocardial infarction or stroke RR: 1.57 (95% CI: 1.26–1.94) and RR: 1.51 (95% CI: 1.24–1.84), respectively [1408]. In an updated meta-analysis on the cardiometabolic effects of ADT, ADT was not associated with metabolic syndrome RR: 1.60 (95% CI: 1.06-2.42), had a lower association with diabetes RR 1.43 (95% CI: 1.28-1.59) as previously reported, and an increased risk of hypertension by 30%, RR 1.30 (95% CI: 1.08-1.55). After adjustment for publication bias ADT was associated with a 25% increased risk for diabetes but was not associated with metabolic syndrome [1409].

An increase in cardiovascular mortality has been reported in patients suffering from previous congestive heart failure or myocardial infarction in a retrospective database analysis [1410] or presenting with a metabolic syndrome [1411]. It has been suggested that antagonists might be associated with less cardiovascular morbidity compared to agonists, but, as yet there is no definite evidence [1320, 1412]. In a phase III RCT the use of relugolix, an oral LHRH antagonist, was associated with a reduced risk of major adverse cardiovascular events when compared to leuprolide, an injectable LHRH agonists, at 2.9% vs. 6.2%, respectively, over a follow-up time of 48 weeks (HR 0.46, 95% CI: 0.24–0.88) [1053].

Concerns about LHRH agonists resulted in an FDA warning and consensus paper from the American Heart, Cancer Society and Urological Associations [1029]. Preventive advice includes non-specific measures such as loss of weight, increased exercise, minimising alcohol intake, improved nutrition and smoking cessation [83, 1413].

The adverse-effects of different ARTAs (abiraterone, apalutamide, darolutamide, enzalutamide) in the treatment of mCRPC, nmCRPC, and mHSPC were systematically reviewed in a multi-variate network meta-analysis. Here it is suggested that the ARTAs adverse effect profiles do not significantly differ from each other, except that enzalutamide was ranked the most toxic regarding hypertension in mCRPC and nmCRPC, and the most toxic regarding headache across all prostate cancer settings [1414].

8.2.5.6 Fatigue

Fatigue often develops as a side effect of ADT. Regular exercise appears to be the best protective measure. Reporting clinically significant fatigue is associated with severe psychological distress and should prompt screening for anxiety and/or depression [1415]. Anaemia may be a cause of fatigue [1375, 1416]. Anaemia requires an aetiological diagnosis (medullar invasion, renal insufficiency, iron deficiency, chronic bleeding) and individualised treatment. Regular blood transfusions may be required in patients with severe anaemia.

8.2.5.7 Neurological side effects

Castration seems also to be associated with an increased risk of stroke [1417], and is suspected to be associated with an increased risk for depression and cognitive decline such as Alzheimer disease [1418].

8.2.5.8 Osteonecrosis during bisphosphonates or denosumab

Bisphosphonates are synthetic pyrophosphate analogs and used in conditions such as malignancy and osteoporosis. Infrequent side effects associated with bisphosphonate use include pyrexia, renal function impairment, hypocalcemia, and avascular osteonecrosis of the jaw. Denosumab is a human monoclonal antibody that is used in the treatment of osteoporosis and bone metastasis [1419, 1420]. It acts by inhibiting osteoclast activity, reducing bone resorption, and increasing bone density [1419]. Its highly specific mechanism of action is the inhibition of receptor activator of nuclear factor-kappa B ligand (RANKL). It has been shown to be effective at increasing bone mineral density and decreasing fractures in men with prostate cancer on ADT [1421].

Both drugs are associated with osteonecrosis of the jaw (ONJ) According to the American Society of Bone and Mineral Research, ONJ is described as exposed bone in the maxillofacial region that does not heal within eight weeks of being identified by a healthcare provider in a patient that is currently or has been on bisphosphonates who does not have a history of radiation therapy in the craniofacial region [1422]. The incidence of ONJ is related to the dose and duration of treatment. The risk ranges from greater than 1% at twelve months to 11% after four years of treatment - taking zoledronic acid alone increases the risk of osteonecrosis to 21% after the third year. A SR on denosumab [1423] showed in a total of 8,963 patients with a variety of solid tumours in seven randomised controlled trials (RCTs) that the overall incidence of ONJ in patients with cancer receiving denosumab was 1.7% [95% CI: 0.9–3.1%]. The use of denosumab was associated with a significantly increased risk of ONJ in comparison with bisphosphonates (BPs)/placebo treatment (RR 1.61, 95% CI: 1.05–2.48, P = 0.029). Subgroup analysis based on controlled therapies demonstrated an increased risk of ONJ in denosumab therapy, when compared with BPs (RR 1.48, 95% CI: 0.96–2.29, p = 0.078) or placebo (RR 16.28, 95% CI: 1.68–158.05, p = 0.017). Similar results were observed for prostate cancer (RR 3.358, 95% CI: 1.573–7.166, p = 0.002). Denosumab combined with risk factors such as dental extraction, poor oral hygiene, use of removable apparatus, and chemotherapy may favour the development of ONJ. Therefore, before starting these drugs the patients should undergo a dental examination and maintain good oral hygiene.

8.3 Overall quality of life in men with PCa

Living longer with PCa does not necessarily equate to living well [1342, 1344]. There is clear evidence of unmet needs and ongoing support requirements for some individuals and partners after diagnosis and treatment for PCa [1424, 1425]. Fear of cancer recurrence and PSA anxiety has a prevalence of 16% and 22%, respectively, across studies [1426]. Combined cognitive- and education-based psychological interventions improve depression, anxiety, and distress [1427]. Cancer impacts on the wider family and cognitive behavioural therapy can help reduce depression, anxiety, and stress in caregivers [1428]. Radical treatment for PCa can negatively impact long-term QoL (e.g., sexual, urinary and bowel dysfunction) as can ADT used in short- or long-term treatment, e.g., sexual problems, fatigue, psychological morbidity, adverse metabolic sequelae and increased cardiovascular and bone fracture risk [1370, 1429]. Direct symptoms from advanced or metastatic cancer, e.g., pain, hypercalcaemia, spinal cord compression and pathological fractures, also adversely affect health [1430, 1431]. Patients' QoL including domains such as sexual function, urinary function and bowel function is worse after treatment for PCa compared to non-cancer controls [1432, 1433]. A PCa diagnosis commonly results in financial strain both for the individual and their families. This financial toxicity is associated with younger age at diagnosis, black race, low socio-economic status, low educational attainment and living in a rural area. Clinicians should discuss financial strains and signpost to support services so that quality of life and adherence to treatment can be maintained [1434].

As QoL is subjective and can mean different things to different people it can be difficult to measure and compare. Nevertheless, there are some generally common features across virtually all patients. Drawing from these common features, specific tools or PROMs have been developed and validated for men with PCa. These questionnaires assess common issues after PCa diagnosis and treatment and generate scores which reflect the impact on perceptions of HRQoL. During the process of undertaking two dedicated SRs around

cancer-specific QoL outcomes in patients with PCa as the foundation for our guideline recommendations, the following validated PROMs were found in our searches (see Table 8.3.1). The tools with the best evidence for psychometric properties and feasibility for use in routine practice and research settings to assess PROMs in patients with localised PCa were EORTC QLQ-C30 and QLQ-PR25. Since EORTC QLQ-C30 is a general module that does not directly assess PCa-specific issues, it should be adopted in conjunction with the QLQ-PR25 module [1435].

Table 8.3.1: PROMs assessing cancer specific quality of life [1435]

Questionnaire	Domains/items
European Organisation for Research and Treatment of Cancer QLQ-C30 (EORTC QLQ-C30) [1436]	Five functional scales (physical, role, cognitive, emotional, and social); three symptom scales (fatigue, pain, and nausea and vomiting); global health status/QoL scale; and a number of single items assessing additional symptoms commonly reported by cancer patients (dyspnoea, loss of appetite, insomnia, constipation and diarrhoea) and perceived financial impact of the disease.
European Organisation for Research and Treatment of Cancer QLQ-PR 25 (EORTC QLQ-PR 25) [1437]	Urinary, bowel and treatment-related symptoms, as well as sexual activity and sexual function.
Functional Assessment of Cancer Therapy-General (FACT-G) [1438]	Physical well-being, social/family well-being, emotional well-being, and functional well-being.
Functional Assessment of Cancer Therapy-Prostate (FACT-P) [1439]	12 cancer site specific items to assess for prostate-related symptoms. Can be combined with FACT-G or reported separately.
Expanded prostate cancer index composite (EPIC) [1440]	Urinary, bowel, sexual, and hormonal symptoms.
Expanded prostate cancer index composite short form 26 (EPIC 26) [1441]	Urinary, sexual, bowel, and hormonal domains.
UCLA Prostate Cancer Index (UCLA PCI) [1442]	Urinary, bowel, and sexual domains.
Prostate Cancer Quality of Life Instrument (PCQoL) [1443]	Urinary, sexual, and bowel domains, supplemented by a scale assessing anxiety.
Prostate Cancer Outcome Study Instrument [1433]	Urinary, bowel, and sexual domains.

*8.3.1 **Long-term (> twelve months) quality of life outcomes in men with localised disease***

8.3.1.1 Men undergoing local treatments

In the updated results of the ProtecT trial [1444] treatment-received analyses revealed different impacts of treatments over six years. Men remaining on AM experienced gradual declines in sexual and urinary function with age with increases in ED from 35% at baseline to 53% at six years and nocturia from 20% to 38%. Radical treatment impacts were immediate and continued over six years. After RP, 95% reported ED persisting for 85% at six years, after EBRT this was 69% and 74%, respectively ($p < 0.001$ compared with AM). After RP, 36% reported urinary leakage requiring at least one pad/day, persisting for 20% at six years, compared with no change in men receiving EBRT or AM ($p < 0.001$). Worse bowel function and bother such as bloody stools 6% at six years and faecal incontinence 10%, was experienced by more men after EBRT than after RP or AM ($p < 0.001$) with lesser effects after BT. No treatment affected mental or physical QoL. In another paper on the twelve years outcome this trial [1364], it was seen that the generic quality-of-life scores were similar in randomised groups over seven to twelve years, urinary leakage requiring pads occurred in 18-24% of patients In the prostatectomy group over seven to twelve years, compared with 9-11% in the AM group and 3-8% in the radiotherapy group. Erections sufficient for intercourse were reported in 18% at seven years in the prostatectomy group, compared with 30% in the AM and 27% in the radiotherapy groups; all converged to low levels of potency by year twelve. Nocturia (voiding at least twice per night) occurred in 34% in the prostatectomy group compared with 48% in the radiotherapy group and 47% in the AM group at twelve years. Faecal leakage affected 12% in the radiotherapy group compared with 6% in the other groups by year twelve. The AM group experienced gradual age-related declines in sexual and urinary function, avoiding radical treatment effects unless they changed management.

Other observational studies [668, 1243, 1354, 1445-1448] also report findings regarding RP and RT. The Prostate Cancer Outcomes Study (PCOS) studied a cohort of 1,655 men, of whom 1,164 had undergone RP and 491 RT [1354]. The study reported that at five years of follow-up, men who underwent RP had a higher prevalence of

urinary incontinence and ED, while men treated with RT had a higher prevalence of bowel dysfunction. However, despite these differences detected at five years, there were no significant differences in the adjusted odds of urinary incontinence, bowel dysfunction or ED between RP and RT at fifteen years. Investigators have reported that although EBRT was associated with a negative effect in bowel function, the difference in bowel domain score was below the threshold for clinical significance twelve months after treatment [1365]. As 81% of patients in the EBRT arm of the study received IMRT, these data suggest that the risk of side effects is reduced with IMRT compared to older 3D-CRT techniques. This is supported by five-year prospective, population-based cohort study where PROMs were compared in men with favourable- and unfavourable-risk localised disease [1447]. In the 1,386 men with favourable risk, comparison between AS and nerve-sparing prostatectomy, EBRT or LDR BT demonstrates that surgery is associated with worse urinary incontinence at five years and sexual dysfunction at three years when compared to AS. External beam RT is associated with changes not clinically different from AS, and LDR BT is associated with worse irritative urinary-, bowel- and sexual symptoms at one year. In 619 men with high-risk localised disease, comparison between non-nerve sparing RP and EBRT with ADT demonstrates that surgery is associated with worse urinary incontinence and sexual function through five years. A SR demonstrates that the risk of post-radiotherapy ED has reduced to a median of 25% at two years with utilisation of IMRT and is now similar to that noted after LDR BT [1449].

A few prospective studies have reported specific long-term urinary functional outcomes after RP and RT even if the studies are not comparative between the two treatment modalities. Considering incontinence and ED after RP the prospective randomised PIVOT trial, comparing RP to observation, reported that 40% of men wore pads, of which 20% wore more than > one pad/day, and an increased rate of ED in the RP group as compared to observation from 70% to approximately 87%, after a median follow-up of 12.7 years [1243]. The corresponding figures from the prospective non-randomised LAPPRO-trial, comparing open- to robot-assisted RP, were 27–29% of the patients reporting urinary incontinence of some degree after eight years and 66–70% reporting ED [1448]. Data on urinary, sexual and bowel function after RT has been reported from the HYPO-RT-PC-trial, a prospective randomised non-inferiority trial comparing ultra-HFX to conventional fractionation RT. In this trial 52–55% of the patients reported urinary problems (RTOG toxicity grade ≥ 1) at five years, of which 4.2–4.7% reported a RTOG grade ≥ 3 urinary morbidity and 7–8% reported moderate-to-severe incontinence at six years. Bowel toxicity of any level (RTOG toxicity grade ≥ 1) was reported in 53–54% of the patients at five years, of which 1.5–1.9% reported a RTOG grade ≥ 3 bowel morbidity, and 66–71% reported to have little or no erection without aids after six years follow-up [668, 1446].

8.3.1.2 Guidelines for quality of life in men undergoing local treatments

Recommendations	Strength rating
Advise eligible patients for active surveillance that global quality of life is equivalent for up to five years compared to radical prostatectomy or external beam radiotherapy (RT).	Strong
Discuss the negative impact of surgery on urinary and sexual function, as well as the negative impact of RT on bowel function with patients.	Strong
Advise patients treated with brachytherapy of the negative impact on irritative urinary symptomatology at one year but not after five years.	Weak

*8.3.2 **Improving quality of life in men who have been diagnosed with PCa***

8.3.2.1 Men undergoing local treatments

In men with localised disease, nurse-led multi-disciplinary rehabilitation (addressing sexual functioning, cancer worry, relationship issues, depression, managing bowel and urinary function problems) provided positive short-term effects (four months) on sexual function (effect size 0.45) and long-term (twelve months) positive effects on sexual limitation (effect size 0.5) and cancer worry (effect size 0.51) [1450].

Exercise programs during RT combined with ADT result in consistent benefits for cardiovascular fitness (standardised mean difference [SMD], 0.83; 95% CI: 0.31–1.36; $p < 0.01$) and muscle function (SMD, 1.30; 95% CI: 0.53–2.07; $p < 0.01$) with a reduction in urinary toxicity (SMD, -0.71; 95% CI: -1.25 to -0.18; $p < 0.01$) [1451]. In men undergoing AS, twelve weeks of high-intensity interval training may improve cardiovascular fitness and suppress PSA progression [1452].

In men with post-surgical urinary incontinence, conservative management options include pelvic floor muscle training with or without biofeedback, electrical stimulation, extra-corporeal magnetic innervation (ExMI), compression devices (penile clamps), lifestyle changes, or a combination of methods. Uncertainty around the effectiveness and value of these conservative interventions remains [1453]. Surgical interventions including

sling and artificial urinary sphincter (AUS) significantly decrease the number of pads used per day and increase the QoL compared with before intervention. The overall cure rate is around 60% and results in improvement in incontinence by about 25% [1454]. Other alternatives, such as the Adjustable Transobturator Male System (ATOMS) and the Adjustable Continence Therapy (proACT) may be an option but seems less efficacious than AUS [1455]. For a more detailed overview of management of urinary incontinence in these men see Chapter 5.6 in the EAU Guidelines for Management of Non-neurogenic Male LUTS [1456].

The use of PDE5 inhibitors in penile rehabilitation has been subject to some debate. A single-centre, double-blind RCT of 100 men undergoing nerve-sparing surgery reported no benefit of nightly sildenafil (50 mg) compared to on-demand use [1457]. However, a multi-centre double-blind RCT (n = 423) in men aged < 68 years, with normal pre-treatment erectile function undergoing either open, conventional or robot-assisted laparoscopic nerve-sparing RP, tadalafil (5 mg) once per day improved participants EPIC sexual domain-scores (least squares mean difference +9.6, 95% CI: 3.1–16.0) when compared to 20 mg 'on demand' or placebo at nine months of follow-up, even though the difference vanished after the end of study [1458]. Therefore, based on discordant results, no clear recommendation is possible, even if a trend exists for early use of PDE5 inhibitors after RP for penile rehabilitation [1459]. A detailed discussion can be found in the EAU Sexual and Reproductive Health Guidelines [1460].

In a SR of genitourinary cancers with mostly prostate cancers it is evident that sexual well-being concerns for men and their partners are evident from diagnosis and into survivorship. Both (patient and partners) benefited from interventions but many articulated difficulties with initiating the topic due to embarrassment and limited access to interventions in cancer services [1461].

Testosterone
Regarding supplementation of testosterone there seems to be some hesitation by HCP. Although the evidence is limited, men who are managed expectantly for PCa, or who received radical local therapy, do not have worse outcomes when receiving testosterone supplementation [77]. We therefore advise to not hesitate to give testosterone substitution to symptomatic hypogonadal men with prostate cancer where ADT is not the treatment of choice.

8.3.2.2 Men undergoing systemic treatments
Similar to men treated with a radical approach (see above), in men with T1-T3 disease undergoing RT and ADT, a combined nurse-led psychological support and physiotherapist-led multi-disciplinary rehabilitation has reported improvements in QoL. Specifically, this intervention involved action planning around patients' needs related to lifestyle changes, weight control, toilet habits, sexuality, and psychological problems. This was complemented with pelvic floor muscle therapy. Improvements in urinary (adjusted mean 4.5, 95% CI: 0.6–8.4), irritative (adjusted mean 5.8, 95% CI: 1.4–10.3) and hormonal (adjusted mean 4.8, 95% CI: 0.8–8.8) EPIC domains were found up to 22 weeks of follow-up [1462]. In a three-year follow-up with 92% response rate from the initial study, fewer participants had moderate-severe bowel problems in the intervention (n = 2; 3%) vs. control group (n = 10; 14%) (p = 0.016) but the benefits in terms of urinary function were maintained only in those participants with moderate-severe urinary problems at baseline [1463].

Providing supervised aerobic and resistance exercise training of a moderate intensity improves EORTC QLQ-C30 role (adjusted mean 15.8, 95% CI: 6.6–24.9) and cognitive domain outcomes (adjusted mean 11.4, 95% CI: 3.3–19.6) as well as symptom scales for fatigue (adjusted mean 11.0, 95% CI: 20.2–1.7), nausea (adjusted mean 4.0, 95% CI: 7.4–0.25), and dyspnoea (adjusted mean 12.4, 95% CI: 22.5–2.3) up to three months in men treated with ADT [1464]. Such interventions have also reported clinically relevant improvements in FACT-P (mean difference 8.9, 95% CI: 3.7–14.2) in men on long-term ADT [1465, 1466]. These findings are supported by a SR which reported improvements up to twelve weeks in cancer-specific QoL in a meta-analysis of high-quality trials (SMD 0.33, 95%, CI: 0.08–0.58) [1416]. Supervised exercise interventions delivered over twelve months are effective in reducing psychological distress; particularly in those men with highest levels of baseline anxiety and depression [1467]. In untrained older men, SR suggests lower volume exercise programs at moderate-to-high intensity are as effective as higher volume resistance training for enhancing body composition, functional capacity and muscle strength and may reduce barriers to exercise and enhance adherence [1468].

Another SR and meta-analysis of randomised trials shows that exercise interventions for patients on ADT result in higher lean body mass (mean difference: 0.88, 95% CI 0.4 to 1.36, p < 0.01), a lower body fat mass (mean difference: -0.93, 95% CI: -1.10 to -0.10, p < 0.05), and a lower body fat rate (mean difference:-0.93, 95% CI: -1.39 to -0.47, p < 0.01). Greater efficacy was noted for exercise duration of ≥ six months (vs. < six months) and exercise immediately after starting ADT (vs. delayed exercise) [1469]. A SR and meta-analysis in patients with prostate cancer undergoing ADT, on supervised exercise therapy vs. no therapy shows that supervised exercise

therapy is probably superior to no exercise therapy in improving 'disease-specific quality of life' 0.43 (95%CI: 0.29, 0.58) and 'walking performance' −0.41 (95% CI: −0.60, −0.22) with a moderate certainty of evidence [1470]. A SR and meta-analysis on determining the factors that affect adherence to exercise programs, found that exercise had no effects ($p < 0.05$) on quality of life and fatigue. For aerobic fitness, and upper- and lower-body strength significant effects (all $p < 0.05$) were observed. Adherence to exercise-based interventions was 80.38%, with improvements observed in aerobic fitness and strength. Subgroup analysis revealed exercise adherence impacted fatigue and strength, with greater improvements observed in programs > twelve weeks [1471].

If dietary intake is not adequate, vitamin D and calcium supplementation should be offered, as there is evidence that vitamin D and calcium have modest effects on bone in men on ADT [1457]. Online tools are available to calculate daily calcium intake for individual patients. For vitamin D deficiency a dose of at least 800 IU/day colecalciferol can be recommended. Use of a 25(OH) assay may be helpful to measure vitamin D levels [1472, 1473].

Anti-resorptive therapy is recommended for men on ADT for > six months with either a BMD T-score of < -2.5 or with an additional risk factor for osteoporosis or annual bone loss confirmed to exceed 5%, or in cases of severe fracture. Referral to a bone specialist should be considered in complex cases with severe fracture and/or multiple risk factors. Alendronate, risedronate, zoledronate and denosumab have all been shown to prevent bone loss in men with hormone-sensitive locally-advanced and metastatic PCa on ADT [1474-1477]. Patients should be warned about the < 5% risk of osteonecrosis of the jaw and/or atypical femoral fractures associated with these drugs. Bisphosphonates increase BMD in the hip and spine by up to 7% in one year [1476, 1478]. The optimal regimen for zoledronic acid for men on ADT with hormone-sensitive locally-advanced and metastatic PCa remains unclear: quarterly [1479] or yearly [1480] injections. The question is relevant as the risk of jaw necrosis is both dose- and time-related [1481]. A quarterly regimen should be considered for a BMD ≤ 2.5 as a yearly injection is unlikely to provide sufficient protection [1482, 1483]. Care should be taken when discontinuing treatment as rebound increased bone resorption can occur.

In M0 patients, denosumab has been shown to increase the lumbar BMD by 5.6% compared to a 1% decrease in the placebo arm after two years, using 60 mg subcutaneous regimen every six months [1421]. This was associated with a significant decrease in vertebral fracture risk (1.5% vs. 3.9%, $p = 0.006$). The benefits were similar whatever the age (< or > 70 years), the duration or type of ADT, the initial BMD, the patient's weight, or the initial BMI. This benefit was not associated with any significant toxicity, e.g., jaw osteonecrosis or delayed healing in vertebral fractures. In M0 patients, with the use of a higher dosage (120 mg every four weeks), a delay in bone metastases of 4.2 months has been shown [1280] without any impact on OS, but with an increase in side effects. Therefore, this later regimen cannot be recommended.

In the SPARTAN phase III study (apalutamide in nmCRPC) [1267], patients receiving apalutamide experienced falls more frequently vs. those receiving placebo (15.6% vs. 9.0%). In the final multivariable model, the baseline patient characteristics of older age, poor ECOG, history of neuropathy, and α-blocker use before study treatment, remained significantly associated with fall. After-baseline clinical characteristics significantly associated with time to fall were development of neuropathy, arthralgia, and weight loss before fall. Preventive interventions should be considered when the identified baseline conditions and post-treatment neuropathy, arthralgia, or weight decrease are present, to reduce risk of fall.

8.3.2.3 Decision regret

Several treatments with curative intent for localised PCa are available all with comparable ten-year OS [489]. They vary in terms of the incidence of major side effects, including urinary symptoms, bowel symptoms and compromised sexual functioning [1364, 1365, 1484]. For this reason, patients' treatment preferences, in which they weigh expected benefits against likely side effects, are a central consideration in shared decision-making and in making informed treatment decisions [1485-1487].

It remains challenging, however, to evaluate whether the decision-making process can be viewed as successful; that is, whether the choice of treatment best reflects the patient's preferences and expectations [1488, 1489]. According to Decision Justification Theory (DJT), it is the more specific information on which treatment experiences lead to regret that decision regret needs to be better understood and to minimise it in future patients [1490]. About 25% of men with PCa undergoing either single or combined modality treatments report experiencing worse side effects than expected [1491]. Urinary incontinence most strongly correlates with regret after prostatectomy [1492].

Unmet expectations are comparable among the treatment groups, except for fatigue. Fatigue is less frequently reported as worse than expected by patients who received BT when compared to patients who received RP or EBRT. This could be explained by the less invasive treatment course of BT in comparison to EBRT

with or without ADT and RP [1493]. Unmet expectations were more frequently reported by patients with positive surgical margins following surgery; having had a passive role in the decision-making process; and who had higher scores on the decisional conflict scale (i.e., more uncertainty about the treatment decision). Interestingly, positive surgical margins are not directly associated with an increased risk of PC-related mortality [960]. Active participation and support in the process of forming a preference increases the chance of choosing a treatment that is in line with patients' expectations [1487, 1494-1496].

While it may seem desirable to tailor the patients' role in decision-making to their initial preference, and particularly to a preference for deferring to the advice of the clinician, this does not result in less decisional conflict or regret. Increasing patients' knowledge regardless of initial preference may actually be preferable [1492].

8.3.2.4 Decision aids in prostate cancer

Shared decision-making can increase patients' comfort when confronted with management decisions but has been shown to improve health outcome [1497] and more training seems needed for health care professionals guiding patients [1498]. Patient education decreased PSA testing [1499] and increased adherence to AS protocols [1500, 1501]. Autonomous active decision-making by patients was associated with less regret after prostatectomy regardless of the method chosen and decision aids reduce decisional conflict [1502]. Still, guidance is needed to optimise patients' understanding of the options [1503]. Patients prioritised effectiveness and pain control over mode of administration and risk of fatigue when confronted with treatment choice in metastasised PCa [1504]. When implementing decision aids clinical validity and utility should be carefully evaluated and distinguished [1505]. A decision aid should educate as well as promote shared decision-making to optimise efficacy [1506] and pay attention to communicative aspects [1507].

8.3.2.5 Guidelines for quality of life in men undergoing systemic treatments

Recommendations	**Strength rating**
Offer men on androgen deprivation therapy (ADT), twelve weeks of supervised (by trained exercise specialists) combined aerobic and resistance exercise.	Strong
Advise men on ADT to maintain a healthy weight and diet, to stop smoking, reduce alcohol to ≤ two units daily and have yearly screening for diabetes and hypercholesterolemia. Ensure that calcium and vitamin D meet recommended levels.	Strong
Offer men after any radical treatment specialist nurse-led, multi-disciplinary rehabilitation based on the patients' personal goals addressing incontinence, sexuality, depression and fear of recurrence, social support and positive lifestyle changes.	Strong
Offer men starting on long-term ADT dual emission X-ray absorptiometry (DEXA) scanning to assess bone mineral density.	Strong
Offer anti-resorptive therapy to men on long term ADT with either a BMD T-score of < -2.5 or with an additional clinical risk factor for fracture or annual bone loss on ADT is confirmed to exceed 5%.	Strong

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10. CONFLICT OF INTERESTS

All members of the EAU-EANM-ESTRO-ESUR-ISUP-SIOG Prostate Cancer Guidelines Panel have provided disclosure statements of all relationships that they have that might be perceived as a potential source of a conflict of interest. This information is publicly accessible through the European Association of Urology website: https://uroweb.org/guideline/prostate-cancer/. This guidelines document was developed with the financial support of the European Association of Urology. No external sources of funding and support have been involved. The EAU is a non-profit organisation and funding is limited to administrative assistance and travel and meeting expenses. No honoraria or other reimbursements have been provided.

11. CITATION

The format in which to cite the EAU Guidelines will vary depending on the style guide of the journal in which the citation appears. Accordingly, the number of authors or whether, for instance, to include the publisher, location, or an ISBN number may vary.

The compilation of the complete Guidelines should be referenced as:
EAU Guidelines. Edn. presented at the EAU Annual Congress Paris April 2024. ISBN 978-94-92671-23-3.

If a publisher and/or location is required, include: EAU Guidelines Office, Arnhem, the Netherlands.
http://uroweb.org/guidelines/compilations-of-all-guidelines/

References to individual guidelines should be structured in the following way:
Contributors' names. Title of resource. Publication type. ISBN. Publisher and publisher location, year.

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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 (TC) represents 5% of urological tumours affecting mostly younger males. This document addresses post-pubertal testicular germ-cell tumours (TGCTs) in the male including spermatocytic tumour 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 references/individual circumstances of patients into account. Guidelines are not mandates and do not purport to be a legal standard of care.

1.2 Panel composition

The European Association of Urology (EAU) Guidelines Panel on TC consists of a multidisciplinary group of clinicians including, urologists, medical oncologists, a radiation-oncologist, patient representative and a pathologist. When necessary, consultants from other specialties provide input. Members of this Panel have been selected, based on their expertise, to represent the professionals' treating patients with TC. All experts involved in the production of this document have submitted potential conflict of interest statements which can be viewed on the EAU website: http://www.uroweb.org/guideline/testicular-cancer/.

1.3 Available publications

A quick reference document (Pocket guidelines) is available, in print and on the EAU website. 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 TC Guidelines. All documents are accessible through the EAU website: https://uroweb.org/guidelines/testicular-cancer.

1.4 Publication history and summary of changes

*1.4.1 **Publication history***

The EAU published the first guidelines on TC in 2001. Since 2008, the TC Guidelines contains a separate chapter on testicular stromal tumours. The 2024 TC guideline presents a limited update of the 2023 publication. A summary paper of the EAU TC guideline has been published in the society's scientific journal European Urology in 2023 [1].

*1.4.2 **Summary of changes***

For the 2024 Testicular Cancer Guidelines, the key changes incorporated in this publication include:

- A restructure and update of section 5.2 on Imaging of primary tumours and staging;
- An update on the summary of evidence table 6.1.2.5;
- Restructure and rewrite of section 6.2.2 on Metastatic disease (stage IIA/B);
- New recommendation regarding the treatment of metastatic NSGCT with a poor prognosis section 6.3.6.1;
- New section 8.5 on follow-up of rare and adult para- and testicular cancers.

2. METHODS

2.1 Introduction

For the 2024 EAU Guidelines on Testicular Cancer (TC), new and relevant evidence was identified, collated and appraised through a structured assessment of the literature. A broad and comprehensive literature search, covering all sections of the TC Guidelines was performed. The search was limited to studies representing high levels of evidence, i.e. systematic reviews with meta-analysis, randomised controlled trials (RCTs), and prospective non-randomised comparative studies, published in the English language. Databases searched included Medline, EMBASE, and the Cochrane Libraries, covering a time frame between May 1st 2021 and May 1st 2023. A total of 1867 unique records were identified, retrieved and screened for relevance.

Detailed search strategies for the 2024 guideline are available online:
https://uroweb.org/guidelines/testicular-cancer/publications-appendices.

Recommendation within the Guidelines are developed by the panels to prioritise clinically important care decisions. The strength of each recommendation is determined by the balance between desirable and undesirable consequences of alternative management strategies, the quality of the evidence (including certainty of estimates), and the nature and variability of patient values and preferences. This decision process, which can be reviewed in the strength rating forms which accompany each guideline statement, addresses a number of key elements:

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

Strong recommendations typically indicate a high degree of evidence quality and/or a favourable balance of benefit to harm and patient preference. Weak recommendations typically indicate availability of lower quality evidence, and/or equivocal balance between benefit and harm, and uncertainty or variability of patient preference [3].

Additional information can be found in the general Methodology section of this print, and online at the EAU website: www.uroweb.org/guidelines.

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

2.2 Review

The 2020 Guidelines document was subjected to peer-review following publication. The next peer-review is scheduled for 2025.

2.3 Future goals

- A collaborative systematic review (SR) on hypogonadism following orchidectomy with the EAU Male Sexual Health guidelines panel;
- The development of a TC survivorship plan in collaboration with patient associations;
- Care Pathways on diagnostic, treatment CS I, and treatment of metastatic disease;
- Collaboration with the patient office and patient representatives to develop a care pathway focusing on what the patient needs to know from diagnosis through to follow-up.

3. EPIDEMIOLOGY, AETIOLOGY & PATHOLOGY

3.1 Epidemiology and Aetiology

Testicular cancer represents 1% of adult neoplasms and 5% of urological tumours, with three to ten new cases per 100,000 males/per year in Western societies [4]. The incidence of TC has increased during recent decades, predominantly in industrialised countries [5-8], and it continues to rise. At diagnosis, 1-2% are bilateral and 90-95% of cases are germ cell tumours (GCT) [4]. The peak incidence is in the third decade of life for non-seminomatous germ cell tumour (NSGCT) and mixed GCT patients, and in the fourth decade for seminoma testis (ST) patients. In 5% of GCT patients, the primary site is at an extragonadal location [9].

There are two fundamental categories of GCTs based on their development and epigenetic features. Most malignant post-pubertal GCTs originate from germ cell neoplasia "*in situ*" (GCNIS). Histologically and clinically, these are subdivided into seminomas and non-seminomas, the latter encompassing somatic and extra-embryonal elements of embryonal carcinoma, yolk sac, choriocarcinoma and post-pubertal teratoma [10].

Non GCNIS derived tumours include pre-pubertal type teratoma and yolk sac tumour, which occur in early childhood, and spermatocytic tumours which usually occurs in older men. Although there is overlapping histology between the pre-pubertal type teratoma/yolk sac and the teratoma and yolk sac tumour elements in the GCNIS-derived NSGCT, these have a separate and independent pathogenesis [10].

Risk factors for GCNIS-derived GCTs are components of the testicular dysgenesis syndrome, which encompasses cryptorchidism, hypospadias, decreased spermatogenesis and impaired fertility [11-13] or disorders of sex development [14]. Additional risk factors include a family history of TC among first-degree relatives and the presence of a contralateral testicular tumour or GCNIS [15-23] although the risk was lower if TC patients previously had received platinum-based chemotherapy [24, 25]. Genome-wide association studies revealed detectable susceptibility loci leading to an increased relative risk to develop TC [26].

3.2 Histological classification

General:
The recommended pathological classification shown below is based on the 2022 update of the World Health Organization (WHO) pathological classification [27].

1. **Germ cell tumours derived from germ cell neoplasia** *in situ*
   - Non-invasive germ cell neoplasia
     - Germ cell neoplasia *in situ*
     - Specific forms of intratubular germ cell neoplasia
     - Gonadoblastoma
   - The germinoma family of tumours
     - Seminoma
   - Non-seminomatous germ cell tumours
     - Embryonal carcinoma
     - Yolk sac tumour, postpubertal-type
     - Choriocarcinoma
     - Placental site trophoblastic tumour
     - Epithelioid trophoblastic tumour
     - Cystic trophoblastic tumour
     - Teratoma, postpubertal-type
     - Teratoma with somatic-type malignancy
   - Mixed germ cell tumours of the testis
     - Mixed germ cell tumours
   - Germ cell tumours of unknown type
     - Regressed germ cell tumours

2. **Germ cell tumours unrelated to germ cell neoplasia** *in situ*
     - Spermatocytic tumour
     - Teratoma, prepubertal-type
     - Yolk sac tumour, prepubertal-type
     - Testicular neuroendocrine tumour, prepubertal-type
     - Mixed teratoma and yolk sac tumour, prepubertal-type

3. **Sex cord stromal tumours of the testis**
   - Leydig cell tumour
     - Leydig cell tumour
   - Sertoli cell tumours
     - Sertoli cell tumour
     - Large cell calcifying Sertoli cell tumour
   - Granulosa cell tumours
     - Adult granulosa cell tumour
     - Juvenile granulosa cell tumour
   - The fibroma thecoma family of tumours
     - Tumours in the fibroma thecoma group
   - Mixed and other sex cord stromal tumours
     - Mixed sex cord stromal tumour
     - Signet ring stromal tumour
     - Myoid gonadal stromal tumour
   - Sex cord stromal tumour NOS

4. Tumours of the testicular adnexa

- Ovarian-type tumours of the collecting ducts and rete testis
  - Serous cystadenoma
  - Serous tumour of borderline malignancy
  - Serous cystadenocarcinoma
  - Mucinous cystadenoma
  - Mucinous borderline tumour
  - Mucinous cystadenocarcinoma
  - Endometrioid tumours
  - Clear cell adenocarcinoma
  - Brenner tumour
- Tumours of the collecting ducts and rete testis
  - Adenoma of the collecting ducts and rete testis
  - Adenocarcinoma of the collecting ducts and rete testis
- Paratesticular mesothelial tumours
  - Adenomatoid tumour
  - Well-differentiated papillary mesothelial tumour
  - Mesothelioma
- Tumours of the epididymis
  - Cystadenoma of the epididymis
  - Papillary cystadenoma of the epididymis
  - Adenocarcinoma of the epididymis
  - Squamous cell carcinoma of the epididymis
  - Melanotic neuroectodermal tumour of the epididymis

4. STAGING & PROGNOSIS

4.1 Staging

The 2016 Tumour, Node, Metastasis (TNM) classification of the International Union Against Cancer (UICC) is recommended to assess the anatomical extent of the disease (Table 1) [28].

Table 1: TNM classification for testicular cancer (adapted from UICC, 2016, 8th edn.) [28]

pT - Primary Tumour[1]	
pTX	Primary tumour cannot be assessed (see note[1])
pT0	No evidence of primary tumour (e.g., histological scar in testis)
pTis	Intratubular germ cell neoplasia (carcinoma *in situ*)+
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 more than 5 nodes positive, none more than 5 cm; or evidence of extranodal extension of tumour
N3	Metastasis with a lymph node mass more than 5 cm in greatest dimension

Pn - Regional Lymph Nodes – Pathological			
pNX	Regional lymph nodes cannot be assessed		
pN0	No regional lymph node metastasis		
pN1	Metastasis with a lymph node mass 2 cm or less in greatest dimension and 5 or fewer positive nodes, none more than 2 cm in greatest dimension		
pN2	Metastasis with a lymph node mass more than 2 cm but not more than 5 cm in greatest dimension; or more than 5 nodes positive, none more than 5 cm; or evidence of extranodal extension of tumour		
pN3	Metastasis with a lymph node mass more than 5 cm in greatest dimension		
M - Distant Metastasis			
MX	Distant metastasis cannot be assessed		
M0	No distant metastasis		
M1	Distant metastasis **		
	M1a Non-regional lymph node(s) or lung metastasis		
	M1b Distant metastasis other than non-regional lymph nodes and lung		
S - Serum Tumour Markers (Pre-chemotherapy)			
SX	Serum marker studies not available or not performed		
S0	Serum marker study levels within normal limits		
	LDH (U/l)	**hCG (mIU/mL)**	**AFP (ng/mL)**
S1	< 1.5 x N and	< 5,000 and	< 1,000
S2	1.5-10 x N or	5,000-50,000 or	1,000-10,000
S3	> 10 x N or	> 50,000 or	> 10,000

N indicates the upper limit of normal.

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 assessed in the radical orchidectomy specimen; see pT. In other circumstances, TX is used if no radical orchidectomy has been performed.

[+] The current "Carcinoma in situ" nomenclature is replaced by GCNIS.

** AJCC eighth edition subdivides T1 Pure Seminoma by T1a and T1b depending on size no greater than 3 cm or greater than 3 cm in greatest dimension [29].*

*** AJCC eighth edition considers hilar soft tissue invasion and epididymal invasion as pT2, while the discontinuous involvement of the spermatic cord is considered as pM1 [29].*

4.2 The Union for International Cancer Control prognostic groups

According to the 2016 TNM classification, the following prognostic groups are defined:

Table 2: Prognostic groups for testicular cancer (UICC, 2016, 8th edn.) [28]

Stage grouping	T	N	M	S
Stage 0	pTis	N0	M0	S0
Stage I	pT1-T4	N0	M0	SX
Stage IA	pT1	N0	M0	S0
Stage IB	pT2 - pT4	N0	M0	S0
Stage IS	Any pT/TX	N0	M0	S1-3
Stage II	Any pT/TX	N1-N3	M0	SX
Stage IIA	Any pT/TX	N1	M0	S0
	Any pT/TX	N1	M0	S1
Stage IIB	Any pT/TX	N2	M0	S0
	Any pT/TX	N2	M0	S1
Stage IIC	Any pT/TX	N3	M0	S0
	Any pT/TX	N3	M0	S1

Stage III	Any pT/TX	Any N	M1a	SX
Stage IIIA	Any pT/TX	Any N	M1a	S0
	Any pT/TX	Any N	M1a	S1
Stage IIIB	Any pT/TX	N1-N3	M0	S2
	Any pT/TX	Any N	M1a	S2
Stage IIIC	Any pT/TX	N1-N3	M0	S3
	Any pT/TX	Any N	M1a	S3
	Any pT/TX	Any N	M1b	Any S

Stage IA: 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-orchidectomy serum tumour marker levels within normal limits. Marker decline in patients with Clinical Stage I (CS I) disease should be assessed until normalisation occurs on two consecutive measurements.

Stage IB: More locally invasive primary tumour, but no sign of metastatic disease.

Stage IS: Following orchiectomy tumour markers increase, remain persistently elevated or fail to decline as expected by half-lives indicating the presence of subclinical metastatic disease. The presence of a second GCT in the contralateral testis should also be excluded.

In population-based patient series from developed countries, 75-80% of SGCT patients, and 55-64% of NSGCT patients had CS I disease at diagnosis [30, 31]. True CS I, i.e. persistently elevated or increasing serum tumour marker levels after radical orchidectomy, was found in approximately 5% of NSGCT patients [30].

4.3 Risk factors for relapse in clinical stage I testicular cancer

For CS I seminoma germ cell tumour (SGCT), primary tumour size and stromal invasion of the rete testis have been identified to be associated with relapse risk in a pooled analysis of retrospective data [32]. Absence of both factors was associated with a low risk of recurrence (6%) [35]. Whilst the original analysis was not supported by a subsequent retrospective report [33], some prospective series [34-36] have supported the prognostic significance of tumour size and stromal invasion of the rete testis. Two SRs assessed the prognostic value of both risk factors [37, 38]. While tumour size (continuous or dichotomised) and rete testis invasion were associated with a higher risk of relapse, both SRs highlighted the low quality of the studies included and concluded that the level of evidence was too low to be able to recommend the use of both risk factors to drive adjuvant treatment decisions [37, 38].

For CS I NSGCT, invasion of the primary tumour into blood or lymphatic vessels, (i.e. lymphovascular invasion (LVI)), was strongly associated with the risk of relapse disease [39-41]. No other risk factors have the same level of validation for prognostic significance [42]. While interobserver agreement is variable, immunohistochemistry with vascular markers may improve detection of LVI [43]. The percentage of embryonal carcinoma within a tumour may enhance the positive predictive value (PPV) and negative predictive value (NPV) of LVI [40], but there is no definitive prognostic cut-off for percentage [40]. Risk of relapse at five years according to historical figures, for patients with LVI-positive tumours was 50% vs. 15% in patients with LVI-negative tumours.

Table 3: Pathological risk-factors for occult metastatic disease in clinical stage I testicular cancer

Histological type	Seminoma [37]	Non-seminoma [41, 44]
• Pathological risk-factors	• Tumour size • Invasion of the rete testis	• Lympho-vascular invasion in peri-tumoral tissue

4.4 The International Germ Cell Cancer Collaborative Group (IGCCCG) classification for the prognostic risk groups of metastatic germ cell cancer

The 1997 IGCCCG defined a prognostic risk-factor system for metastatic GCT based on identification of clinically independent adverse factors [45]. The classification has been revalidated on a contemporary cohort of metastatic TGCT treated with cisplatin/etoposide based first-line chemotherapy [46].

Compared to the 1997 figures, the five-year progression-free survival (PFS) of NSGCT patients was unchanged for good- and intermediate-risk, but significantly improved for poor-risk patients (from 41% to 54%). The five-year overall survival (OS) was substantially better for all groups. In addition to the traditional components of the IGCCCG risk-prognostic groups previously described, older age (linear association) and lung metastases were confirmed as negative factors for PFS [46].

For SGCT, revalidation of the IGCCCG classification showed that the five-year PFS increased to 89% and 79% in good- and intermediate-risk patients with corresponding OS rates of 95% and 88%. Testicular lactate dehydrogenase (LDH) over 2.5 times the upper limit of normal (ULN) was identified as a possible adverse prognostic factor in regard to reduced three-year PFS, however overall three-year survival was not affected [47].

Table 4: Prognostic-based staging system for metastatic germ cell cancer (IGCCCG) [46, 47]*

Good-prognosis group	
NSGCT 5-year PFS 90% 5-year survival 96%	*All of the following criteria:* • Testis/retro-peritoneal primary • No non-pulmonary visceral metastases • AFP < 1,000 ng/mL • β-hCG < 5,000 IU/L (1,000 ng/mL) • LDH < 1.5 x ULN
SGTC 5-year PFS 89% 5-year survival 95%	*All of the following criteria:* • Any primary site • No non-pulmonary visceral metastases • Normal AFP • Any β-hCG • Any LDH
Intermediate-prognosis group	
NSGCT 5-year PFS 78% 5-year survival 89%	*Any of the following criteria:* • Testis/retro-peritoneal primary • No non-pulmonary visceral metastases • AFP 1,000 - 10,000 ng/mL or • β-hCG 5,000 - 50,000 IU/L or • LDH 1.5 - 10 x ULN
SGCT 5-year PFS 79% 5-year survival 88%	*All of the following criteria:* • Any primary site • Non-pulmonary visceral metastases • Normal AFP • Any β-hCG • Any LDH
Poor-prognosis group	
NSGCT 5-year PFS 54% 5-year survival 67%	*Any of the following criteria:* • Mediastinal primary • Non-pulmonary visceral metastases • AFP > 10,000 ng/mL or • β-hCG > 50,000 IU/L (10,000 ng/mL) or • LDH > 10 x ULN
SGCT	No patients classified as poor-prognosis

** Pre-chemotherapy serum tumour markers should be assessed immediately prior to the administration of chemotherapy (same day).*

AFP = alpha-fetoprotein; β-hCG = human chorionic gonadotrophin; LDH = lactate dehydrogenase; PFS = progression-free survival.

5. DIAGNOSTIC EVALUATION

5.1 Physical examination

Testicular cancer usually presents as a painless testicular mass or incidental finding on ultrasound (US). Pain, either scrotal or abdominal/back, may occur and result in delayed diagnosis [48]. Gynaecomastia may be present in a small number of patients. Clinical assessment should thus include abdominal, chest and supraclavicular examination.

5.2 Imaging

*5.2.1 **Primary tumour***

The primary tumour and contralateral testis need to be assessed radiologically to

1. confirm the presence of a mass;
2. determine whether it is intra- or extra-testicular;
3. assess its volume and anatomical location;
4. characterise the contralateral testicle – to exclude other lesions and identify risk factors for GCNIS (see section 5.4.4).

High-frequency (>10 MHz) testicular US is recommended. Scrotal US is also recommended for all men with retroperitoneal or visceral masses with/or without elevated serum β-hCG or Alpha-fetoprotein (AFP) in the absence of a palpable testicular mass [49].

Small, usually non-palpable masses may be incidental findings on scrotal US which may be benign. Of lesions with small diameter virtually all < 3mm, 87% of those < 5mm and 70% < 10mm are benign [50-52]. With small masses US features may assist in discriminating between benign and malignant tumours although none are completely reliable [50].

Scrotal magnetic resonance imaging (MRI) provides higher sensitivity and specificity than US in the diagnosis of TC, but its high cost does not justify its routine use for this purpose [53]. It should only be considered when US is inconclusive as local staging for potential testis-sparing surgery (TSS), to differentiate between paratesticular and intratesticular lesions, and/or to characterise intratesticular masses (e.g., distinctive features of Leydig tumours) [53].

*5.2.2 **Staging***

Cross-sectional imaging of the chest, abdomen and pelvis is recommended in patients with elevated markers or clinical suspicion of metastases for staging before orchidectomy and remains standard practice. This may be postponed in patients with small or indeterminant masses until histopathological confirmation of malignancy. Contrast enhanced CT scan (CECT) and MRI are the imaging modalities used. Evidence does not support the use of Fluorodeoxyglucose-positron emission tomography (FDG-PET) for initial staging of TC [54, 55].

a. Abdomen and Pelvis

Contrast enhanced CT scan is the long-established imaging modality used to assess the abdomen and pelvis to identify nodal and visceral metastases. The size of metastases should be described in three dimensions, or at least by the greatest diameter. The expected patterns of nodal spread in TC should be considered when evaluating small and borderline nodes.

A SR of a number of small studies, with a total of 102 evaluable patients, has suggested that MRI appears comparable to CECT in detecting nodal metastases [56]. It is significantly more expensive and less available than CECT for routine use. It clearly has utility in patients who have contra-indications to iodine-based contrast media or likely to require numerous subsequent scans.

b. Thorax

The chest and supraclavicular fossa should also be imaged with CECT to assess for nodal and pulmonary disease. Magnetic resonance imaging appears equivalent to CT in detecting supra-diaphragmatic lymph nodes but less sensitive in detecting pulmonary nodules. Thus, it is not recommended as a routine alternative to CT [57].

c. Other Sites

Cerebral and spinal imaging is recommended in GCT patients with either multiple lung metastases or poor-prognosis IGCCCG risk group (especially with β-hCG values > 5,000 UI/L), or clinical symptoms [58]. Data from cerebral and spinal metastasis detection in other malignancies suggest that MRI is far more sensitive than CECT but requires specific expertise [59, 60]. When available, MRI should be used to evaluate for both cerebral and spinal metastases in GCTs if there are clinical concerns. Contrast enhanced computerised tomography may be used if MRI is not available or contraindicated.

5.3 Serum tumour markers

*5.3.1 **Pre-operative serum tumour markers***

Serum AFP, beta subunit of human Chorionic Gonadotropin (β-hCG) and LDH should be determined before orchidectomy as they support the diagnosis of TC and may be indicative of GCT histology.

Up to 90% of NSGCT's have elevated AFP or β-hCG at diagnosis with 39% having an increased level of both [48, 61]. Pure seminomas may also have elevated β-hCG level at diagnosis in up to 30% of cases [61]. Significant elevation of AFP in patients with seminomas should raise concerns of a NSGCT component. Modest stable marker elevations may be considered 'normal' and of no clinical significance [45].

Thus, current tumour markers have limitations due to their low sensitivity as normal levels do not exclude the presence of disease.

*5.3.2 **Serum tumour markers after orchidectomy***

Tumour markers need to be repeated following orchidectomy providing staging and prognostic information [45]. If elevated pre-operatively normalisation may take several weeks as the serum half-lives of AFP and β-hCG are five to seven days and one to three days respectively. If these remain elevated or increase metastatic disease is likely [61]. Marker normalisation after orchiectomy however does not exclude the possibility of metastatic disease.

In addition to staging marker levels are used to define risk stratification and prognosis (Table 4). They are also used to monitor treatment response and detect disease relapse [61]. With follow-up the precise frequency of testing is not well defined [62].

*5.3.3 **Other tumour markers***

Micro RNAs (miRNAs) are emerging as potential new biomarkers. Pre-operative elevation has been reported in 80-90% of both SGCT and NSGCT with higher levels in metastatic compared to localised disease [63]. A number of studies suggest higher discriminatory accuracy for micro-RNA (miRNAs) (particularly miR-371a-3p) compared to conventional GCT markers in diagnosis, clinical staging, treatment monitoring, and predicting of residual or recurrent viable disease [63-65]. Furthermore, they may differentiate between GCT and other (stromal/non-germ cell originated) tumours [65]. Issues which need to be resolved for use in routine clinical practice include laboratory standardisation, availability of the test and, importantly, prognostic validation [66]. As with both AFP and β-hCG miRNA is not expressed in teratoma which will limit its use in NSGCT.

5.4 Inguinal exploration and initial management

*5.4.1 **Orchidectomy***

Orchidectomy including division of the spermatic cord at the internal inguinal ring represents the standard of care for patients with a TGTC. A scrotal approach should be avoided when TC is suspected as it results in a higher local recurrence rate [67].

*5.4.2 **Testis-sparing surgery***

In men with GCTs, orchidectomy represents the standard of care as pathological studies describe multifocal and/or adjacent GCNIS in 20-30% of patients [68]. Testis sparing surgery when feasible, may be considered in synchronous bilateral tumours or in tumours in solitary testis [69]. In these settings, at least two additional testicular biopsies should be taken to exclude GCNIS [70].

Testis-sparing surgery (TSS) is a valid treatment option in men with interstitial cell or benign testicular tumours and may prevent hypogonadism and infertility in young men. These tumours are often small although larger lesions may be difficult to differentiate from GCT.

Thus, TSS may be considered in patients with small or indeterminate testicular masses, negative tumour markers and a normal contralateral testis to avoid over-treatment of potentially benign lesions and preserve testicular function [69, 71]. Patients should be informed that cancer may be present even in small (i.e., < 1 cm) masses [69, 72, 73].

In both settings, TSS should be offered together with frozen section examination (FSE). Frozen section examination has shown to be reliable and highly concordant with final histopathology in expert hands, with a 99% and 96% of sensitivity and specificity respectively and 98% and 97% of PPV and NPV, respectively [71]. In cases of discordance between FSE and final pathology delayed orchiectomy may be required.

In cases of a history of GCT or indeterminate small testicular lesion, patients should be made aware of the following issues regarding TSS practice: that limited data exists regarding oncological safety of TSS; that local recurrence rates have been reported (up to 26.9%), when TC is present in the specimen [69, 74] and that TSS has implications for ongoing surveillance of the testis. Similarly, patients should be informed about the role and impact of adjuvant radiotherapy when GCNIS is present, potential infertility, the need for hormonal supplementation despite parenchyma preservation [69, 75] and that discordance between FSE and final pathology requiring a delayed orchidectomy.

*5.4.3 **Insertion of testicular prosthesis***

Testicular prosthesis should be offered to all patients receiving unilateral or bilateral orchidectomy [76]. The prosthesis can be inserted at orchidectomy or subsequently without adverse consequences, including infection [77].

*5.4.4 **Contralateral biopsy***

Contralateral biopsy has been advocated to exclude GCNIS [78] and routine policy in some countries [79]. It is, however, controversial to recommend routine contralateral biopsy in all patients due to the low incidence of GCNIS and metachronous contralateral testicular tumours (up to 9% and approximately 2.5%, respectively) [80, 81], the morbidity of GCNIS treatment (see section 6.1.1), and the fact that most metachronous tumours are low stage at presentation [82, 83]. Nevertheless, the risks and benefits of biopsy of the contralateral testis should be discussed with TC patients at high risk for contralateral GCNIS, i.e., testicular volume < 12 mL, and/or a history of cryptorchidism. Contralateral biopsy is not necessary in patients > 40 years without risk factors [70, 84, 85]. Patients should be informed that a subsequent GCT may arise despite a negative biopsy [86]. When indicated, a two-site surgical testicular biopsy is the technical procedure recommended [70].

5.5 Pathological examination of the testis

The recommendations for reporting and handling the pathological examination of a testis neoplasm are based on the recommendations of the International Society of Urological Pathology (ISUP) [39, 44, 87, 88].

Mandatory pathological requirements:

- *Macroscopic features:* It must indicate radical or partial orchidectomy, side, testis size, number of tumours, and macroscopic features of the epididymis, cord length, and tunica vaginalis.
- *Sampling:* At least a 1 cm^2 section for every centimetre of maximum tumour diameter including normal macroscopic parenchyma (if present), tunica albuginea and epididymis, with selection of suspicious areas. If the tumour is < 20 mm it should be completely sampled.
- At least one proximal (base of the cord) and one distal section of spermatic cord plus any suspicious area. Cord blocks should preferably be taken prior to tumour sections to avoid contamination.
- *Microscopic features and diagnosis:* Histological types (specify individual components and estimate amount as percentage) according to WHO 2022 [27]:
  - Presence or absence of peri-tumoral lymph and/or blood vessel invasion. In case of doubt, the use of endothelial markers, such as CD31, are recommended.
  - Presence or absence of GCNIS in non-tumour parenchyma.
  - In case of rete testis invasion attention should be paid to distinguishing between pagetoid involvement and stromal invasion [44].
- If microscopic findings are not concordant with serum markers further block samples should be taken.
- Pathological tumour (pT) category according to TNM 2016 [28]. In a multifocal seminoma the largest nodule should be used to determinate pT category.

Immune-histochemical markers in cases of doubt are:

- Seminoma: CD-117 (c-KIT), OCT 3/4, Sall4, PLAP
- GCNIS: CD-117 (c-KIT), OCT 3 / 4, Sall4, PLAP
- Syncytiotrophoblastic: β-hCG
- Embryonal carcinoma: CD30
- Yolk sac tumour: Glypican 3, AFP.
- Sex cord gonadal tumours: Inhibin, calretinin steroidogenic factor 1.

The search for i12p (FISH or PCR) or gain in Chr9 (spermatocytic tumour) are additional molecular techniques which are only rarely required. Confirmation of the utility of other molecular markers such as P53, MDM2, KRAS and HRAS is awaited [89].

In order to facilitate consistent and accurate data collection, promote research, and improve patient care, the International Collaboration on Cancer Reporting has constructed a dataset for the reporting of urological neoplasms. The dataset for testicular tumours encompasses the updated 2016 WHO classification of urological tumours, the ISUP consultation and staging with the 8th edition of the American Joint Cancer Committee (AJCC) [88].

The dataset includes those elements unanimously agreed by the expert panel as "required" (mandatory) and those "recommended" (non-mandatory) that would ideally be included but are either non-validated or not regularly used in patient management [88]. The dataset for handling pathological assessment of TC is shown in Table 5.

Table 5: Recommended dataset for reporting of neoplasia of the testis (modified from the International Collaboration on Cancer Reporting) [88]

Elements	Required	Recommended*	Content	Remarks
Clinical information		√	- Not provided - Previous history of testicular cancer - Previous therapy - Other	Specify each
Serum tumour markers		√	- Not provided - If provided within normal limits or - Specify serum tumour markers used - Specify levels - Specify date markers were drawn	Select all that apply: Serum tumour markers: LDH (IU/L), AFP (ug/L), β-hCG (IU/L)
Operative procedure	√		- Not specified - Orchidectomy partial - Orchidectomy radical - Other	Specify side for partial or radical orchidectomy. Specify other
Tumour focality	√		- Cannot be assessed - Indeterminate - Unifocal - Multifocal	If multifocal specify number of tumours in specimen.
Maximum tumour dimension	√		- Cannot be assessed - Dimensions largest tumour (mm) - Dimensions additional tumour nodules#	Specify at least maximum diameter of largest tumour. Preferably specified 3 dimensions/axes.#

Macroscopic extent of invasion	√		- Cannot be assessed - Confined to testis - Invades epididymis - Invades tunica vaginalis - Invades hilar structures - Invades spermatic cord - Invades scrotum - Other	Select all that apply. If other specify.
Block identification key		√	N/A	List overleaf or separately with indication of nature and origin of all tissue blocks.
Histological tumour type	√		- Germ cell tumour: type and percentage - Other	Use WHO classification (2022) update [27]. If other specify.
Microscopic extent of invasion	√		- Rete testis of stromal/ interstitial type - Epididymis - Hilar fat - Tunica albuginea# - Tunica vaginalis - Spermatic cord - Scrotal wall	For all: - not submitted - not involved - involved
Lymphovascular extension	√		- Not identified - Present	If present specify type.#
Intratubular lesions (GCNIS)	√		- Not identified - Present - Other intratubular lesions#	If other intratubular lesions present identify type.#
Margin status	√		- Partial orchidectomy: . cannot be assessed . involved . not involved - Radical orchidectomy: . cannot be assessed . spermatic cord margin involved . spermatic cord margin not involved - Other margin involved	In partial orchidectomy if margin not involved, distance of tumour from closest margin (mm).# If other margin involved specify.
Coexisting pathology		√	- None identified - Hemosiderin-laden macrophages - Atrophy - Other	If other specify
Ancillary studies		√	- Not performed - Performed	If performed specify
Response to neoadjuvant therapy		√	- Present - Absent - No prior treatment - Cannot be assessed	Explain reasons if cannot be assessed.
Pathologic staging*	√		T classification according to TNM 8th edition (UICC)**	m-multiple primary tumours r-recurrent y-post-therapy

** Not mandatory. Ideally to be included but either non-validated or no regularly used in patient management.*

*** TNM 8th edition (AJCC) used in the original publication.*

 # Recommended, i.p. intratubular seminoma and embryonal carcinoma.

5.6 Screening

No high-level evidence studies supporting screening programs exists [90, 91]. In contrast young males should be informed about the importance of testicular self-examination. Testicular self-examination is recommended in high-risk groups which include a history of cryptorchidism, as well as those with a personal or family history of TC [90, 92].

5.7 Summary of evidence and recommendations for the diagnosis and staging of Testicular Cancer

Summary of evidence	LE
Poor sperm quality is frequently found in TC patients, before and after treatment. Semen preservation is the most cost-effective strategy for fertility preservation.	2b
Serum tumour markers (AFP, β-hCG and LDH) should be determined before and after orchidectomy and throughout follow-up. They are used for accurate staging, risk stratification, to monitor treatment and to detect relapse.	2b
For abdominal staging, CECT has a median sensitivity, specificity, PPV, NPV and accuracy of 67%, 95%, 87%, 73% and 83%, respectively. Sensitivity decreases and specificity increases with increasing lymph node size.	2a
For chest staging, CECT has a median sensitivity, specificity, PPV, NPV and accuracy of 100%, 93%, 68%, 100% and 93%, respectively.	2a
Magnetic resonance imaging and CECT are key image modalities for the detection of brain metastasis. Magnetic resonance imaging is far more sensitive than CECT, though it does require expertise.	2b
Fluorodeoxyglucose-positron emission tomography has a limited diagnostic accuracy for staging before chemotherapy.	2b
There are no high-level evidence studies supporting screening programs.	2b
In testicular sparing surgery, FSE has shown to be reliable and highly concordant with final histopathology.	1b
There is no evidence supporting any size criteria for a testicular lesion to be safely followed-up.	2b
In patients without risk factors, there is low incidence of contralateral GCNIS and of metachronous GCT.	2b

Recommendations	Strength rating
Discuss sperm banking with all men prior to starting treatment for testicular cancer (TC).	Strong
Perform bilateral testicular ultrasound (US) in all patients with suspicion of TC.	Strong
Perform physical examination including supraclavicular, cervical, axillar, and inguinal lymph nodes, breast, and testicles.	Strong
Measure serum tumour markers both before and after orchidectomy taking into account half-life kinetics.	Strong
Perform orchidectomy and pathological examination of the testis to confirm the diagnosis and to define the local extension (pathological tumour (pT) category). In a life-threatening situation due to extensive metastasis, commence chemotherapy prior to orchidectomy.	Strong
Perform contrast enhanced computerised tomography (CECT) scan (chest, abdomen, and pelvis) in patients with a diagnosis of TC. In case of iodine allergy or other limiting factors perform abdominal and pelvic magnetic resonance imaging (MRI).	Strong
Perform MRI of the brain (or brain CECT if not available) in patients with multiple lung metastases, or high beta subunit of human Chorionic Gonadotropin (β-hCG) values, or those in the poor-prognosis International Germ Cell Cancer Collaborative Group (IGCCCG) risk group.	Strong
Do not use positron emission tomography–computed tomography or bone scan for staging.	Strong
Encourage patients with TC to perform self-examination and to inform first-degree male relatives of the need for self-examination.	Weak
Discuss testis-sparing surgery with frozen section examination in patients with a high likelihood of having a benign testicular tumour which are suitable for enucleation.	Strong
Discuss biopsy of the contralateral testis to patients with TC and who are at high-risk for contralateral germ cell neoplasia "*in situ*".	Strong

6. DISEASE MANAGEMENT

6.1 Stage I germ cell tumours

6.1.1 ***Germ cell neoplasia "in situ" (GCNIS)***

If GCNIS is diagnosed and the contralateral testis is normal, options include orchidectomy or close observation, as the five-year risk of developing TC is 50% [93]. In a solitary testis, local radiotherapy (18-20 Gy in fractions of 2 Gy) should be considered [94-97]. Radiotherapy to a solitary testis will result in infertility and increased long-term risk of Leydig cell insufficiency [94]. Fertile patients who wish to father children may defer radiation therapy and be monitored with regular testicular US [70].

Chemotherapy is ineffective to reliably irradicate GCNIS [98, 99].

6.1.2 ***Seminoma germ cell tumour clinical stage I***

Up to 20% of CS I SGCT patients have subclinical metastatic disease, usually in the retroperitoneum, and will relapse after orchidectomy alone [100, 101]. Adjuvant treatment decisions should be based on thorough discussions with the patient, incorporating potential risks and benefits, as well as individual patient circumstances, as 80% of unselected CS I SGCT patients are cured by orchidectomy alone. Regardless of management, survival in CS I disease is almost 100% [102].

6.1.2.1 Surveillance

This requires a strict protocol of repeated cross-sectional imaging, monitoring of serum tumour markers and clinical assessment for the early identification of patients experiencing relapse who must receive salvage treatment (See Table 11).

Several prospective, non-randomised surveillance studies have been conducted over the past decade. These have shown an overall risk of relapse in unselected CS I patients of 12-20% at five years with 17% in the largest series of over 1,500 patients [103]. Most occur in the retroperitoneum during the first two years [104, 105].

According to a SR, active surveillance offers almost identical overall survival as adjuvant management strategies, approaching 100% [102].

The cancer-specific survival (CSS) rate on "active surveillance" (AS) for CS I seminoma is over 99% [103, 105, 106]. Whilst cost effective compared to other management strategies [107], surveillance can represent a burden to the patient due to the need for repeated imaging of the retroperitoneum and clinic visits. These may negatively impact patient compliance which is crucial to an active surveillance strategy.

6.1.2.2 Adjuvant chemotherapy

An RCT comparing one cycle of carboplatin reaching area under curve of 7 mg/mL/min (AUC 7) to adjuvant radiotherapy (RT) showed no difference in relapse-free rates (95% and 96%), time to recurrence and survival after a median follow-up of four years [108]. Adjuvant carboplatin (AUC 7) is therefore an alternative to RT or surveillance in CS I SGCT [108]. Time to relapse after Carboplatin may be longer than with AS, as retrospective data reported a median time to relapse of nineteen months, with 15% of relapses occurring beyond three years. Most patients relapsing after adjuvant carboplatin can be successfully treated by standard, stage-adapted cisplatin-based chemotherapy [109]. In some selected cases, retroperitoneal lymph-node dissection may be adopted in specific protocols (see below).

One cycle of adjuvant carboplatin does not seem to have significant long-term toxicities. In a series of 199 CS I SGCT patients, there was no increase in overall mortality, mortality from cardiovascular events and no excess of haematological or non-testicular solid malignancies compared to the general population in the UK [110].

6.1.2.3 Adjuvant radiotherapy

Radiotherapy should generally be reserved for a highly selective group of patients, who would be unsuitable for systemic chemotherapy in the event of relapse. This relates to the toxicity of RT, specifically the long-term risk of non-germ cell malignancies in the radiation field [111-114]. Generally, adjuvant RT should be avoided, particularly in young patients with a long life expectancy.

Risk-adapted treatment
Prospective trials based on tumour size > 4 cm and stromal rete testis invasion have demonstrated the feasibility of a risk-adapted approach [33-36, 115].

A trial of 897 patients offered surveillance to patients with no or one of these two risk factors whilst patients with both risk factors were offered one dose of carboplatin, AUC 7 [36]. At a median follow-up of 5.6 years, the patients without risk factors, 4% of surveillance relapsed compared to 2% after adjuvant carboplatin. With one or both risk factors 15.5% of surveillance patients relapsed vs. 9% receiving adjuvant carboplatin. Thirty-three per cent of relapses after adjuvant carboplatin occurred more than three years after orchidectomy with 3% occurring after five years [36].

6.1.2.4 Summary of evidence and recommendations for the treatment of clinical stage I seminoma germ cell tumour of the testis

Summary of evidence	**LE**
Patients with CS I SGCT have, in general, a low risk of recurrence	2a
A combination of tumour size category and rete testis invasion correlate with the risk of relapse at 5 years.	2a
Evidence and ease of use are limited for a routine use in guiding adjuvant treatment decisions upon risk factors.	2a
Active surveillance is a feasible approach with conditional relapse risk in unselected series of between 12-20%. Disease-free survival approaches 100% independently of treatment.	2a
In patients without conventional risk factors (tumour size < 4 cm and no rete testis invasion), the five-year relapse rate under surveillance is up to 6-8%, respectively; whereas in the presence of one or two risk factors, five-year relapse rate in contemporary surveillance series is 15-20%.	2b
In non-randomised prospective series five-year relapse rates with adjuvant carboplatin are 2% in patients without conventional risk factors and 9% in patients with one or both risk factors.	2b
Adjuvant chemotherapy with one course carboplatin AUC 7 is not inferior to adjuvant radiotherapy when pathological risk factors are considered. Relapse rates with both adjuvant treatments are around 5%.	1b
Adjuvant radiotherapy is associated with an increased risk of developing secondary non-germ cell malignancies.	2b

Recommendations	**Strength rating**
Fully inform the patient about all available management options, including surveillance or adjuvant therapy after orchidectomy, as well as treatment-specific recurrence rates and acute and long-term side effects.	Strong
Offer surveillance as the preferred management option if resources are available and the patient is compliant.	Strong
Offer one dose of carboplatin at area under curve 7 if adjuvant chemotherapy is considered.	Strong
Do not perform adjuvant treatment in patients at very low risk of recurrence (no risk factors).	Strong
Do not routinely perform adjuvant radiotherapy.	Strong
Adjuvant radiotherapy should be reserved only for highly selected patients not suitable for surveillance and with contraindication for chemotherapy.	Strong

*6.1.3 **Non-seminomatous germ cell tumours clinical stage I***
Management options for CS I NSGCTs include surveillance and adjuvant chemotherapy. Retroperitoneal lymph node dissection has a limited role.

Overall, approximately 70% of CS I NSGCTs are cured with orchiectomy alone. In those with the high-risk feature of LVI, historical figures reported relapse in 50% compared to 15% in those without LVI. A thorough discussion should be undertaken with the patient outlining the potential advantages and disadvantages of treatment options, as well as individual co-morbidities, disease features, risk factors, specific circumstances, and personal preferences, to guide their treatment decision.

6.1.3.1 Surveillance

Surveillance for CS I NSGCT entails a strict protocol of repeated cross-sectional imaging, monitoring of serum tumour markers and clinical assessment for the early identification of patients experiencing relapse who must receive salvage treatment (See Table 11).

The largest reports of surveillance indicate a cumulative relapse risk in about 30% of CS I NSGCT (five-year conditional risk of relapse 42% and 17% for high- and low-risk CS I-NSGCT, respectively) [101, 103]. Of these, 92% present within the first two years [101, 103, 116-118].

6.1.3.2 Retroperitoneal lymph node dissection

Since the introduction of cisplatin-based chemotherapy the role of adjuvant primary retroperitoneal lymph node dissection (RPLND) in men with CS I NSGCTs has decreased. According to data from high-volume and expert centres, primary RPLND is associated with a risk of relapse < 15% [119]. More recent data report on a relapse rate of 10% in case of negative nodes (pathologic stage (PS) – I) and < 30% in case of nodal metastases (PS II) [119-121], possibly due to selection or stage migration.

The few indications in CS I disease include men with teratoma with somatic malignant component, or patients who are not willing or suitable to undergo chemotherapy in case of recurrence, in particular in those when vascular invasion is present.

Recent publication supports the safety of surveillance alone, in PS II disease following RPLND, as 75-80% are relapse free at two and five years [120-122]. Those with relapse can be rescued with standard chemotherapy [123, 124]. With PS II, both adjuvant chemotherapy comprising two cycles of (B)EP (except for cases of ppt (post pubertal teratoma) only) and AS are standard option to be discussed with each individual.

Strategies to reduce the morbidity of primary RPLND include nerve-sparing and minimally invasive approaches. In a multi-centre setting, higher rates of in-field recurrences and complications have been reported with nerve-sparing RPLND [125, 126]. This suggests that primary RPLND, when indicated and chosen, should be performed by an experienced surgeon in a specialist centre. Minimally invasive (laparoscopic or robot-assisted) primary RPLND, appears feasible and safe (e.g., low-complication rate) in experienced hands. This must only be performed in high-volume RPLND centres with appropriate minimal-invasive surgery expertise [127-134]. There is limited recent data on mid-term follow-up.

Despite some advantages, including good efficacy, a less-demanding and costly follow-up due to the reduced need for cross-sectional imaging [135], RPLND for CS I NSGCT has diminished its role in view of the high CSS rates of surveillance, the low relapse rates with adjuvant chemotherapy, and the lower reproducibility of primary RPLND on a large scale.

6.1.3.3 Adjuvant chemotherapy

Adjuvant chemotherapy has been evaluated with both one and two cycles of BEP (cisplatin, etoposide, bleomycin) in CS I NSGCT. A prospective trial from 1996, as well as subsequent studies, used two cycles of BEP in high-risk patients (LVI present) [136-138]. In these series, including 200 patients, some with a median follow-up of nearly 7.9 years [136], a relapse rate of only 2.7% was reported, with minimal long-term toxicity. Two cycles of cisplatin-based adjuvant chemotherapy do not appear to adversely affect fertility or sexual activity [139].

Other studies have shown one cycle of adjuvant BEP results in similar very low recurrence rates (2-3%) [140, 141]. Reduction from two to one cycle of BEP improves the risk-benefit ratio of adjuvant chemotherapy considerably. A randomised phase III trial has also compared two-year recurrence free survival with adjuvant BEP x 1 to RPLND. Results favoured chemotherapy with recurrence free survival of 99.5% vs. 91% [126]. No clinically relevant differences in quality of life (QoL) were detected [142].

A community based prospective study of 490 unselected patients with CS I NSGCT that received adjuvant single cycle BEP had five-year relapse rates of 3% and 2% for LVI+ and LV- patients, respectively. After a median follow-up of eight years these rates were sustained, no relapses were observed beyond 3.3 years [140, 141]. These numbers imply that > 90% of relapses are prevented by single cycle BEP which is now the recommended strategy if adjuvant chemotherapy is considered [140, 141]. The very-long term (> 20 years) side effects of adjuvant chemotherapy, particularly cardiovascular, are yet to be fully defined and this should be considered during shared decision-making [143, 144].

Limited data are available on outcomes with relapse after adjuvant BEP. A retrospective analysis indicated that about one third of these relapses were late and that the outcome may be slightly worse compared to those presenting with *de novo* metastatic disease [145].

6.1.3.4 Risk-adapted treatment

A risk-adapted strategy is an alternative to any single approach for patients with CS I NSGCT. The advantages and disadvantages of treatment options must be discussed with patients in the context of their specific circumstances including disease risk factors, co-morbidities, and personal preference, as well as clinician recommendation in reaching a treatment decision. Lympho-vascular invasion is the strongest and most reproducible predictive factor for relapse and should be carefully outlined to the patient to assist in their decision-making.

Patients without LVI should be guided to consider surveillance, although some patients with significant co-morbidities or concerns regarding salvage chemotherapy with multicycle cisplatin-based chemotherapy may opt for adjuvant therapy. Those with LVI should have their high risk of relapse (up to 50%) highlighted and be guided to consider adjuvant management, and chemotherapy with BEP X 1 as the "preferred" option.

Some patients may wish to consider primary RPLND although they need to be aware of the potential additional requirement of adjuvant chemotherapy if nodes contain active disease (pN1), as well as the 10% risk of systemic relapse, even if pN0, requiring subsequent chemotherapy treatment (BEP X 3).

6.1.3.5 Post-pubertal teratoma with somatic malignant component

A multi-institutional study analysing retrospective datasets of CS I patients with post-pubertal teratoma with somatic malignant component (TSMC) suggested these patients had inferior five-year OS of approximately 10% compared to other CS I GCT patients. Furthermore, CS I TSMC cases undergoing primary RPPLND had a much higher proportion of nodal metastases (PS II) than expected (37.5%). Despite its limitations, this study provides the only evidence on this issue and supports primary RPLND in CS I NSGCT with TSMC [146].

For patients presenting with CS I pure post-pubertal teratoma without a somatic malignant component, surveillance provides comparable survival outcomes to primary RPLND [147]. A mixed population based study on 237 CS I with pure teratoma in the testis, showed an increasing trend favouring surveillance over RPLND as well as a not significant difference in overall survival at a median follow-up of 54 months [147].

However, subtype discrepancies in primary diagnostic of post-pubertal teratoma are not infrequent and consist in addition of subtype and involve secondary somatic type of malignancy in 83% of cases. As such, central review by expert genitourinary pathologist is recommended when teratoma is diagnosed in the orchidectomy specimen [148].

6.1.3.6 Summary of evidence and recommendations for the treatment of clinical stage I non-seminoma germ cell tumour of the testis

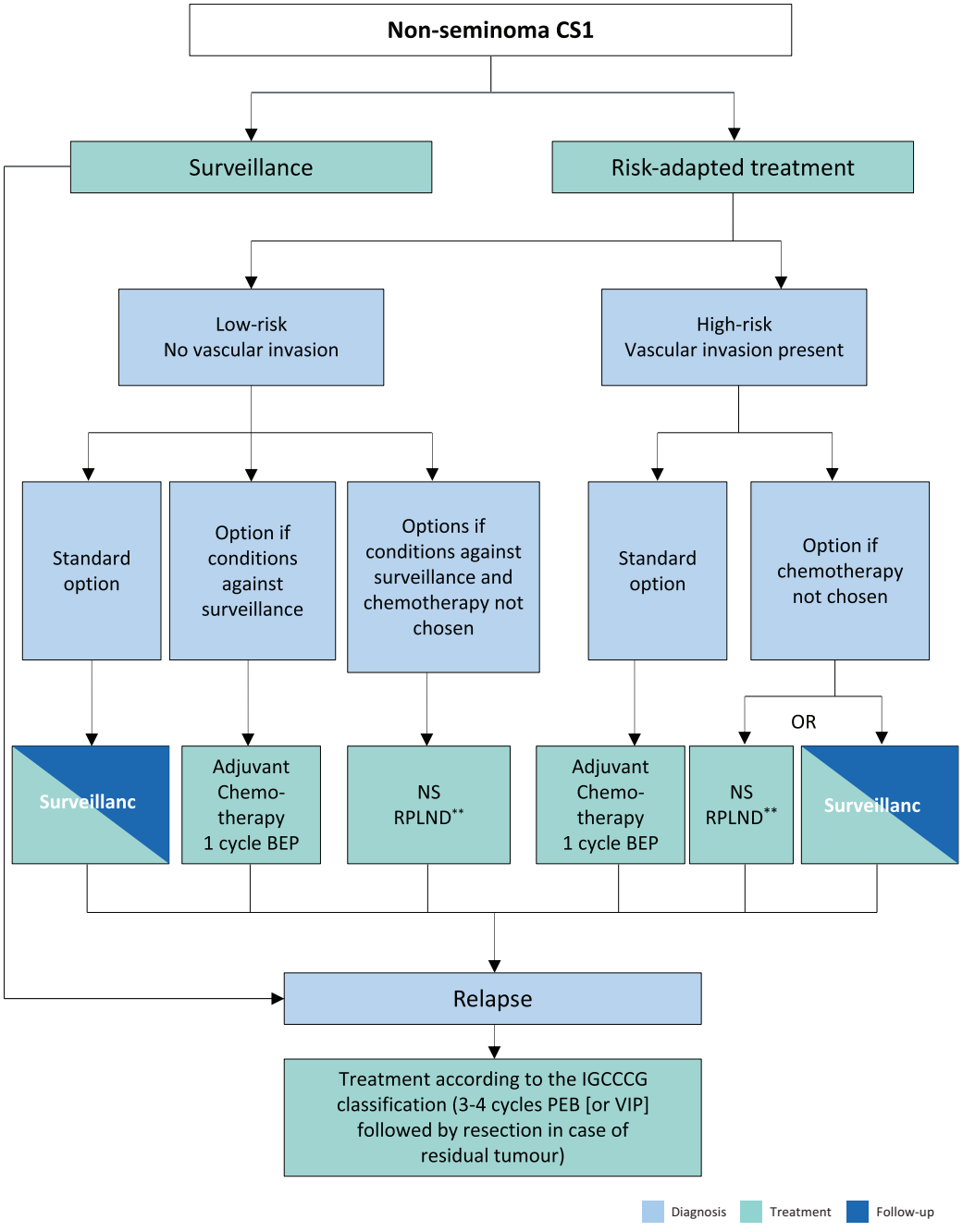
Summary of evidence	**LE**
Lymphovascular invasion increases the risk of relapse.	2a
The relapse rate with active surveillance is up to 50%, when LVI is present.	2a
The relapse rate in patients who receive adjuvant chemotherapy with BEP (x 1 cycle) is up to 3%.	2a
Adjuvant chemotherapy with BEP x 1 is superior to adjuvant RPLND in terms of the risk of relapse when the 2 strategies are not centralised in expert centres.	1b
A risk-adapted approach, based on LVI invasion is feasible.	2b
The acute toxicity of one cycle adjuvant BEP is low.	1b

Recommendations	**Strength rating**
Inform patients about all management options after orchidectomy: surveillance, adjuvant chemotherapy, and retroperitoneal lymph node dissection, including treatment-specific recurrence rates as well as acute and long-term side effects.	Strong
Offer surveillance or risk-adapted treatment based on lymphovascular invasion (see below).	Strong
Discuss one course of cisplatin, etoposide, bleomycin as an adjuvant treatment alternative in patients with stage I non-seminomatous germ cell tumour if patients are not willing to undergo or comply with surveillance.	Strong

6.1.3.7 Recommendations for risk-adapted treatment for clinical stage I non-seminomatous germ cell tumour based on vascular invasion

Recommendations	Strength rating
Stage IA (pT1, no vascular invasion): low risk	
Offer surveillance if the patient is willing and able to comply.	Strong
Offer adjuvant chemotherapy with one course of cisplatin, etoposide, bleomycin (BEP) in low-risk patients not willing (or unsuitable) to undergo surveillance.	Strong
Stage IB (pT2-pT4): high risk	
Offer adjuvant chemotherapy with one course of BEP, or surveillance and discuss the advantages and disadvantages.	Strong
Offer surveillance to patients not willing to undergo adjuvant chemotherapy.	Strong
Offer nerve-sparing retroperitoneal lymph node dissection to highly selected patients only; those with contraindication to adjuvant chemotherapy and unwilling to accept surveillance.	Strong

Figure 1: Risk-adapted treatment in patients with clinical stage I non-seminoma NSGCT*



** Discuss all treatment options with individual patients, to allow them to make an informed decision as to their further care.*
*** In case of PS II, the rate of recurrence is higher and chemotherapy can be administered (max. 2 cycles).*
BEP = cisplatin, etoposide, bleomycin; CS = clinical stage; IGCCCG = International Germ Cell Cancer Collaborative Group; NS = nerve-sparing; RLNPD = retroperitoneal lymph node dissection; VIP = etoposide, cisplatin, ifosfamide.

6.2 Metastatic germ cell tumours

The first-line treatment of metastatic GCTs depends on:

I. the histology of the primary tumour;
II. prognostic groups as defined by the IGCCCG (Table 4) [45];
III. serum tumour marker decline at the end of the first cycle of chemotherapy in poor-prognosis patients.

In relapsed patients, a prognostic score has been developed including response to first-line therapy which can be used to estimate patient outcome following salvage chemotherapy [149].

*6.2.1 **Clinical stage I with (persistently) elevated serum tumour markers***

With elevated markers and CS I, weekly measurement of markers are recommended. If AFP or β-hCG increase or fail to normalise following orchidectomy, US examination of the contralateral testicle must be performed. If a contralateral tumour is excluded, unequivocal rising tumour markers indicates CS I, and treatment for good prognosis metastatic GCT should be given. With stable markers, a new staging procedure, 4-6 weeks after orchidectomy, is recommended.

Some patients may have stable but slightly elevated AFP or β-hCG and can be initially monitored. Treatment should be commenced if markers rise or when follow-up imaging demonstrates metastatic disease.

The treatment of true CS I SGCT should be the same as other metastatic GCT. With this, ten-year overall survival of 95%, have been reported [150, 151].

*6.2.2 **Metastatic disease (stage IIA/B)***

6.2.2.1 Stage IIA/B seminoma

Patients with enlarged retroperitoneal lymph nodes < 2 cm in greatest diameter and normal markers may be observed for six to eight weeks with repeat-staging imaging as these may be non-metastatic on average in 10% of cases. Treatment should only be initiated if metastatic disease is unequivocal, based on biopsy, increasing nodal size/number, or subsequent marker rise [46, 150]. A special case are those patients who can undergo primary RPLND within a trial or institutional study (see below for further details).

Historically, radiotherapy has been the primary treatment for stage II A/B seminoma, showing relapse rates between 9-24% [152, 153]. Recommended radiation doses for stage IIA and IIB are 30 Gy and 36 Gy, respectively. With these doses, five-year relapse-free survival rates stand at 92% for stage IIA and 90% for IIB [152, 153]. A reduced dose of 27 Gy for stage IIA has been associated with a higher relapse rate [105].

Chemotherapy is a standard option for stage IIA/B seminoma, with relapse rates of 0-8% for stage IIA disease and 8-14% for stage IIB disease, and an excellent overall survival of 99% [154, 155]. The standard regimen in stage II seminoma is BEP x 3 (see Appendix 4.1.2) or EPx4 if there are concerns with the use of bleomycin [156]. There are no randomised studies comparing radiotherapy and chemotherapy. A meta-analysis of thirteen high-quality studies, comparing efficacy and toxicity of radiotherapy and chemotherapy showed that these appeared similarly effective in both stage IIA/IIB patients although with a non-significant trend towards greater efficacy for chemotherapy (HR: 2.17) in stage IIB seminoma [154]. Acute toxicity was almost exclusively reported following chemotherapy, while long-term toxicity was more frequent following radiotherapy, mainly comprising bowel toxicity and secondary cancers, generally in the irradiated field [154]. Several series have shown an increased risk of developing a second solid cancer of 1.8-2.0-fold with radiotherapy [157]. Long term toxicities of chemotherapy including second cancers are also a concern [157].

6.2.2.1.1 Retroperitoneal lymph node dissection

Several institutional series and a few single-arm phase II studies have explored primary RPLND with or without adjuvant chemotherapy as an alternative to chemotherapy in men with low volume CS II A/B [158-162]. Differences in surgical technique/template, extent of use of adjuvant chemotherapy, patient selection, and length of follow-up make direct comparisons of these surgical series to chemotherapy difficult. In these reports, patients with low-volume CS II A/B seminoma had two-year recurrence rates of 5-30%, with immature OS outcomes owing to short follow-up. Relapse will almost always be cured by standard chemotherapy. Longer

follow-up and ideally, comparative prospective studies are required to ensure this can be recommended as a safe stand-alone treatment option equivalent to chemotherapy alone.

Primary RPLND for men with low volume CS II seminoma should only be performed by surgeons with extensive experience in specialised TC centres. Ideally, the procedure should take place within a prospective cohort or clinical trial in order to maintain surgical quality and monitor long-term oncological outcomes.

6.2.2.1.2 De-escalating approaches

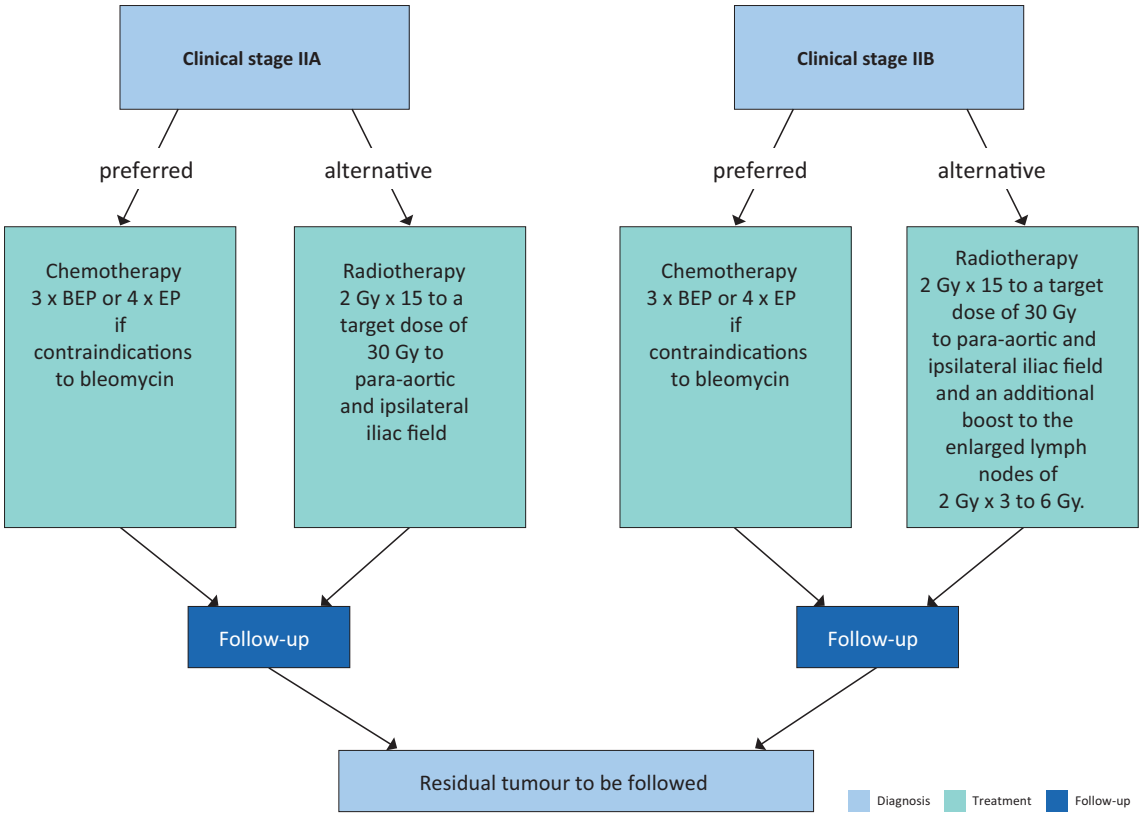
Several trials attempted to de-escalate chemotherapy and RT, aiming at maintaining the traditional excellent oncologic result, while minimising treatment burden and toxicity.

Such an approach was evaluated in a phase II randomised trial, assessing chemotherapy de-escalation in patients guided by metabolic response on FDG-PET/CT after two initial cycles of etoposide, cisplatin (EP) chemotherapy [163]. Patients with complete metabolic response after EP x 2 received de-escalated treatment with one subsequent cycle of carboplatin AUC7, whilst patients with residual metabolic activity completed the initial schedule of EP x 4. The study showed comparable three-year PFS rate of 90% and 91% for the EP and carboplatin groups respectively, and a two-year OS of 100% for both groups. Despite the apparently maintained oncological efficacy, larger studies and longer follow-up is needed. For these reasons and owing to the absence of consensus criteria for FDG-PETC/CT interpretation, making treatment decisions based solely on FDG-PET/CT responses is not currently recommended for routine use [163].

Another de-escalation option emerged, involving one cycle of carboplatin followed by involved-node (small-volume) radiotherapy (30 Gy in 15 sessions for stage IIA and 36 Gy in 18 sessions for stage IIB). This approach has shown a three-year progression-free survival rate of 93.7% in a single-arm phase II trial, narrowly missing its target primary endpoint of 95% three-year PFS [164]. Currently such approaches lack the level of evidence needed for routine use recommendation.

Summary of evidence	**LE**
At this stage all de-escalation strategies, including RPLND remain under evaluation and should only be considered in high volume specialised centres within a prospective cohort or clinical trial.	3

Figure 2: Treatment options in patients with seminoma clinical stage IIA and B*



**when enlarged retroperitoneal lymph nodes are < 2 cm and with normal markers, treatment should not be initiated unless metastatic disease is unequivocal based on biopsy, increasing nodal size/number, or subsequent marker rise.*
BEP = cisplatin, etoposide, bleomycin; EP = etoposide, cisplatin.

6.2.2.2 Stage II A/B non-seminoma (NSGCT)

6.2.2.2.1 Serum tumour marker negative

Patients with normal markers and equivocal lymph nodes (< 2 cm) may be considered for initial surveillance with early re-evaluation at six weeks. If the lesion progresses or fails to resolve it should be regarded and treated as CS II.

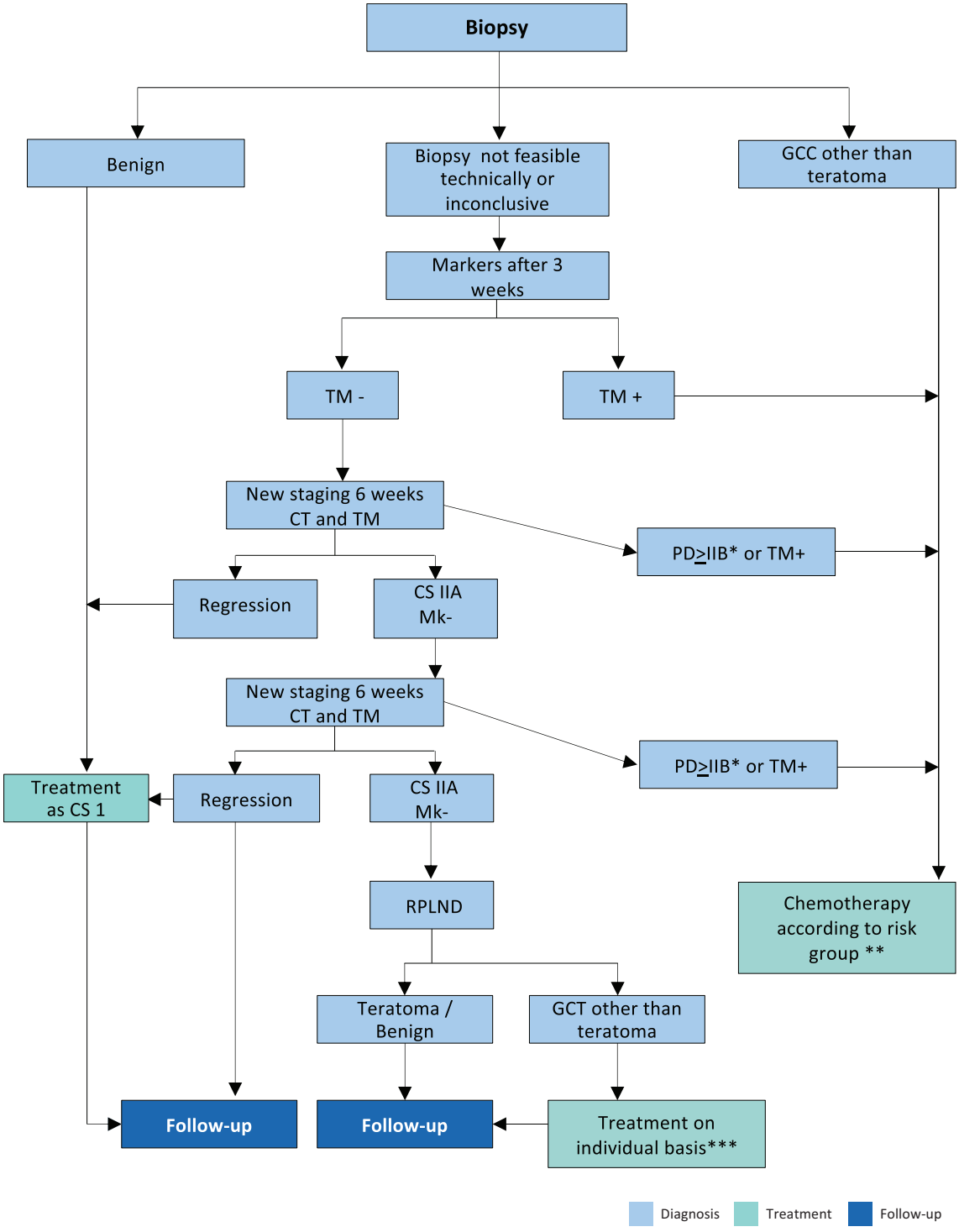
With CS IIA NSGCT disease and normal or normalised tumour markers, nerve sparing RPLND performed by an experienced surgeon in a specialised centre is the recommended initial treatment. Patients may be down staged to PS I in up to 20% of cases and require no further treatment. Patients with post-pubertal teratoma alone will avoid unnecessary chemotherapy as surgery alone is curative. The oncological outcomes after RPLND in CS II NSGCT have been evaluated in a SR [165]. Of the included studies the majority were retrospective with included patients differing substantially in histopathology, size and number of retroperitoneal lymph nodes resected, surgical templates, and the use of adjuvant chemotherapy. In men with marker negative CS II NSGCT, PS II is confirmed in 80%. Without adjuvant chemotherapy 12-40% recurred compared to 0-4% in those who received adjuvant chemotherapy.

These findings align with large single centre reports of outcomes following RPLND alone for PS II NSGCT with active disease [116, 123, 124, 166]. These studies reported five-year relapse of less than 30%, with the majority occurring outside the retroperitoneum requiring systemic chemotherapy according to risk group.

Adjuvant chemotherapy may be discussed with the patient to reduce the risk of relapse in this setting. Key issues include risk factors for relapse (as positive lymph node-ratio), the risk of overtreatment in up to 70% of cases and the need for rigorous follow-up. When adjuvant chemotherapy is chosen, standard treatment is BEP or EP for a maximum of two cycles [165, 167].

A recent single institution real world study including 61 CS IIA/B < 3cm NSGCT (out of 66 GCT) with active disease, showed a 77% two-year progression-free survival without adjuvant chemotherapy in stage IIA/B < 3 cm, with the greatest benefit was achieved in stage IIA marker negative cases [166].

Figure 3: Flowchart Nonseminoma CS IIA Mk- at Diagnosis/Staging



** Most of the patients will be good prognostic group (BEP x3 or PE x4).*
TM – tumour markers
** With marker negative PD > IIB RPLND may be considered if radiological features of teratoma*
*** Most will be good prognostic group (BEP x3 or EP x4) - see Appendix 4*
https://uroweb.org/guidelines/testicular-cancer/publications-appendices.
****In case of PS II A/B patient can be followed-up or receive adjuvant chemotherapy (maximum of 2 cycles).*

6.2.2.2.2 Serum tumour marker positive

Patients with elevated tumor markers and radiological stage IIA/B at diagnosis or relapse should be treated with chemotherapy as outlined in tables 6 and 7 and section 6.2.3.1 based on IGCCCG risk group. Most patients will have a good prognosis for whom BEPX3 is most appropriate or EP x 4 if there are concerns with the use of bleomycin.

Primary RPLND for CS IIA/B disease with elevated markers is not recommended outside a specific study in a referral centre [166, 168].

*6.2.3 **Metastatic disease (stage II C and III)***

6.2.3.1 Primary chemotherapy

6.2.3.1.1 Good-prognosis risk group - seminomatous germ cell tumour

For metastatic seminoma, a cisplatin-based regimen should be used. A cisplatin-based combination chemotherapy has shown superior efficacy over carboplatin-based regimens [169]. The standard regimen in good-risk seminoma is three, twenty-one days cycles of BEP (Table 6). Alternatively, EP x 4 may be considered especially when bleomycin is contraindicated [170]. This achieves similar response rates but may have a slightly higher risk of relapse.

Post-chemotherapy masses should be managed as described in Section 6.5.2.

6.2.3.1.2 Intermediate-prognosis risk group - seminomatous germ cell tumour

For patients with intermediate-risk seminoma, BEP x 4 is the standard regimen. In bleomycin is contraindicated the combination of etoposide, cisplatin, ifosfamide (VIP) should be given. No RCT has focused specifically on this rare group of patients (see Table 4).

6.2.3.1.3 Good-prognosis risk group - non-seminomatous germ cell tumour

The standard regimen in good-risk non-seminoma is BEP x 3 (Table 6) [170].

An RCT support the equivalence of three or five-day regimes with three or four cycles of BEP for projected two-years PFS. Three-day regimes are associated with increased toxicity [171, 172]. Based on these data the BEP x 3 as a five-day regimen is strongly recommended in the good-prognosis risk group.

Two RCTs support the superiority of BEP x 3 over other regimes or schedule intensities [156, 173]. A further RCT has suggested that when EP is used, the mortality rate is twice that of with BEP, although the difference did not reach statistical significance [156].

Patients with a clear contraindication to bleomycin may receive EP x 4 [171]. In all other cases omission of bleomycin is not recommended.

For more information regarding Chemotherapy protocols, please visit the EAU guidelines website:
https://uroweb.org/guidelines/testicular-cancer/publications-appendices

6.2.3.1.4 Intermediate-prognosis risk group - non-seminomatous germ cell tumour

The standard regimen is BEP x 4 [174]. Four cycles of VIP has similar efficacy but is more myelotoxic [175]. Four cycles of VIP including primary G-CSF prophylaxis should be applied in patients with contraindications to bleomycin.

6.2.3.1.5 Poor-prognosis risk group - non-seminomatous germ cell tumour

The standard regimen is four cycles of BEP. Four cycles of VIP have similar efficacy, but is more myelotoxic [175]. Four cycles of VIP including primary granulocyte colony stimulating factor (G-CSF) prophylaxis should be applied in patients with contraindications to bleomycin [176, 177].

Serum tumour marker decline is the only prospectively confirmed predictor for response to cisplatin chemotherapy in metastatic germ cell tumour patients. Patients with inadequate tumour marker decline after the first or second cycle of BEP represent a prognostically inferior subgroup [177, 178]. There are several ways to calculate tumour marker decline kinetics with an example available at:
https://www.gustaveroussy.fr/calculation-tumor/NSGCT.html.

An RCT demonstrated improved PFS when intensifying treatment with dose-dense chemotherapy in patients with an early unfavourable tumour marker decline [179]. The trial was not powered to estimate OS differences. Based on the results from this trial, patients with an unfavourable tumour marker decline after BEP x 1 can be switched to a more intensive (dose-dense) chemotherapy regimen [179]. Additional patient groups with an unfavourable prognosis on standard treatment are primary mediastinal non-seminoma and patients with brain metastases at initial diagnosis [100, 180]. These may also be candidates for upfront intensified treatment, preferably in a prospective study.

In RCTs, primary high-dose chemotherapy (HDCT) with subsequent autologous stem cell transplantation has not shown an OS benefit in the overall poor-prognosis patient population in RCTs [176, 177]. Selected patients, such as primary mediastinal nonseminoma, do have poor survival following standard dose chemotherapy [181]. They may derive a benefit from primary HDCT [182], preferably within a prospective protocol.

Better outcomes are reported for intermediate and poor prognosis patients treated at high-volume centres [183-185]. Due to their unfavourable survival, poor-prognosis patients should be managed at centres with interdisciplinary germ cell tumour expertise and treated in ongoing prospective trials or registries, whenever possible.

There are no general recommendations for treatment modifications for patients with poor performance status (Karnofsky < 50%) or extended liver infiltration (> 50%), although two small patient series indicate that an initial cycle of dose-reduced therapy may reduce acute mortality without compromising long-term outcomes. The number of subsequent cycles of full-dose therapy should, however, not be reduced after an initial low-dose induction cycle [184, 186].

Patients with widespread pulmonary metastases are at risk for pulmonary haemorrhage and subsequent acute respiratory distress syndrome (ARDS) with induction chemotherapy. To reduce this risk, primary cytoreductive induction chemotherapy with EP over two to three days should be administered, followed by the first cycle of standard chemotherapy when the risk of ARDS has passed (typically after ten days) [184].

Table 6: Level of evidence for prognostic group and treatment

Prognostic group IGCCCG	Treatment	LE
Good (SGCT and NSGCT)	BEP x 3 or EP x 4	1b
Intermediate (SGCT and NSGCT)	BEP x 4 or VIP x 4	1b
Poor (NSGCT)	BEP x 4 or VIP x 4 if favourable marker decline	1b
	Dose escalation in selected cases with inadequate serum tumour marker decline	1b

6.2.3.1.6 Prevention of thromboembolism events during chemotherapy

Some RCTs have assessed the risks and benefits of thromboprophylaxis in ambulatory cancer patients receiving chemotherapy and report a relative risk reduction of 30-60% in venous thromboembolic events (VTE) at the cost of a doubling in bleeding risk [187-190]. Based on these results, the most recent American Society of Clinical Oncology (ASCO) Clinical Practice Guideline Update recommends thromboprophylaxis with apixaban, rivaroxaban, or low molecular weight heparin (LMWH) to cancer patients with a high risk of VTE and low risk of bleeding [191]. Metastatic germ cell tumour (mGCT) patients were under-represented in all trials and thus, it is not clear whether this recommendation applies to this group although retrospective data suggests a similar efficacy of VTE prophylaxis [192].

The EAU Guideline panel has discussed a recommendation regarding thromboprophylaxis. All members agreed that men with mGCTs undergoing cisplatin-based chemotherapy are at high-risk for VTE, and with the exception of those with choriocarcinoma and high volume extra-peritoneal disease, are at low risk of bleeding. Given the apparent high VTE incidence* and only non-validated VTE risk factors, the panel preferences were divided between those panel members that favoured thromboprophylaxis in all men and those panel members that restricted thromboprophylaxis to men with certain risk factors. Additionally, the majority of the panel agreed that a central venous-access device should be avoided whenever possible as this represents the only modifiable risk factor, which remained significantly associated with VTE in a multivariable risk-prediction model [193, 194].

**For more information regarding the prevention of thromboembolism events during chemotherapy, please see appendix 2, available online https://uroweb.org/guidelines/testicular-cancer/publications-appendices.*

6.2.3.1.7 Summary of evidence and recommendations for the prevention of thromboembolism events during chemotherapy

Summary of evidence	LE
Thromboembolic events occur more frequently in male patients with GCTs receiving chemotherapy than in young males under chemotherapy for other cancers.	2b
Retrospective studies have identified multiple risk factors for the development of thromboembolic events including increasing stage, size of retroperitoneal lymph nodes at different cut-offs, Khorana score > 3 and indwelling vascular access device (only modifiable risk factor).	2b

Recommendations	Strength rating
Balance the individual patients' potential benefits and risks of thromboprophylaxis during first-line chemotherapy in men with metastatic germ cell tumours.	Weak
Avoid use of central venous-access devices during first-line chemotherapy whenever possible.	Weak

6.3 Treatment evaluation and further treatment

*6.3.1 **Treatment evaluation***

Response to treatment should be assessed after the initial induction cycle by repeat imagining and/or re-evaluation of tumour markers. With marker decline and/or radiologically regressing or stable tumour features, the planned chemotherapy should be completed [192, 194]. If markers decline, but metastases progress on imaging, induction therapy must be completed [195]. If markers have normalised and masses with features of post-pubertal teratoma progress early surgical resection should be considered.

Slow marker-decline with the initial one to two cycles of chemotherapy warrants consideration for dose intensification (see https://www.gustaveroussy.fr/calculation-tumor/NSGCT.html).

Following completion of treatment, cases with a low-level β-hCG plateau should be observed to determine whether complete normalisation subsequently occurs. In patients with a low plateau serum AFP level after chemotherapy, removal of residual masses should be undertaken, with subsequent AFP monitoring. Preoperative AFP levels of > 30 µg/l and viable cancer found in the histological examination of the resected specimen have been described as predictors of relapse after first line chemotherapy [196]. Salvage chemotherapy is thus only indicated for documented marker progression [195, 197].

*6.3.2 **Residual tumour resection***

6.3.2.1 Seminoma

A residual mass of seminoma should initially be monitored with imaging and tumour markers [198-200].

As FDG-PET has a high NPV, in patients with residual masses > 3 cm in largest diameter, this should be considered in order to provide more information on disease viability [201-203]. It should not be performed until at least two months after completion of chemotherapy, as inflammation and the desmoplastic reaction induced by chemotherapy may result in a false positive result [204]. The NPV for active disease is > 90% which can be reassuring [201, 202]. In contrast PPV ranges from 23-69% and thus caution is advised on initiating active therapy driven only by positive findings on FDG-PET-CT [205].

When a post-chemotherapy mass remains positive at reclassification with FDG-PET with no volume increase, repeat FDG-PET should be performed six weeks later. A recent publication shows a low PPV for vital tumours in residual lesions (generally > 3 cm) after chemotherapy in metastatic seminoma (11-38% depending on sub-group). Therefore, caution is recommended with FDG-PET as a single parameter to drive clinical decisions in a persistent mass [205]. In patients with progressive disease on radiological criteria (i.e., a growing mass which enhances with CECT or is FDG-PET avid), salvage therapy is indicated [206-208].

Patients with persistently high and/or progressing β-hCG elevation after first-line chemotherapy should proceed to salvage chemotherapy. Progressing patients without β-hCG progression should undergo histological verification (e.g., by percutaneous or surgical biopsy) before salvage chemotherapy is given. When RPLND is indicated, this should be performed in referral centres, as residual seminoma masses may be extremely difficult to remove due to intense fibrosis [207].

6.3.2.2 Non-seminoma

Following first-line BEP it has be reported that about 7% of residual masses contain active cancer, 33% post-pubertal teratoma, and 40% necrotic-fibrotic tissue only [209]. The remainder comprise rarer entities including malignant transformation of teratoma. Restaging patients following chemotherapy with FDG-PET is not indicated [54, 55, 204]. With complete radiological remission, RPLND is not indicated [210, 211].

Usual timing for restaging is three to four weeks after the beginning of the last cycle. No diagnostic or risk calculator can accurately predict histology of the residual masses. Thus, resection is mandatory in all patients with a residual mass > 1 cm in transaxial long axis at cross-sectional CECT imaging until novel predictive models are externally validated [212-215]. Surgery when indicated should be performed within six to eight weeks after the last chemotherapy cycle.

The role of surgery with residual retroperitoneal lesions < 1 cm is uncertain. It is difficult to distinguish between a true residual node below 10 mm and a complete remission, and many authors consider these situations as equivalent. Residuals containing cancer or teratoma are possible, but the vast majority of patients have fibro-necrotic tissue only [216]. Whilst post-chemotherapy RPLND with residuals < 10 mm in transaxial long axis or complete remission is an option [217], the alternative option is close surveillance with recurrence risk of 6-9% depending on the follow-up duration [209-211, 218]. In the series with the longest follow-up of 15.5 years, twelve (9%) of 141 patients relapsed despite a complete response following primary treatment [211, 218]. Eight of the twelve relapsing patients were cured with subsequent treatment. These cases should be discussed on individual basis considering the orientation and expectations of the patient.

Residual masses after salvage chemotherapy or HDCT in first or subsequent salvage situations have a greater risk of active disease [219]. Surgery is therefore indicated even with residual masses < 1 cm [210, 211].

When resection is indicated, bilateral nerve sparing RPLND is the standard option. Ipsilateral template resection avoids contralateral nerve dissection and may be considered for residuals with a diameter < 5 cm [220], as well as unilateral lymph node metastases on pre- and post-chemotherapy CT scans, left-sided tumours only require para-aortic resection whereas right-side tumours need paracaval and inter-aortocaval resection down to the iliac arteries [221, 222]. Mapping studies indicate the potential risk of contralateral disease with this approach is low at around 1-3% [221, 223]. The mere resection of the residual tumour (so called lumpectomy) should not be performed [211, 215, 216, 219, 220, 222, 224].

Laparoscopic or robotic RPLND may yield comparable outcomes to open procedures in selected cases, with low-volume residual disease and when undertaken by highly experienced surgeons. This should only be considered in specialist TC centres with expertise in open RPLND and minimally invasive surgery to ensure appropriate case selection. In this setting, up to 30% of post-chemotherapy RPLND have been reported via a laparoscopic approach [225-227]. Experience with robot-assisted laparoscopic RPLND, and specifically long-term outcomes remains limited [228]. Atypical recurrences have been reported and occur more often with this approach [128].

6.3.3 ***Sequencing of surgery in the case of multiple sites***

In general, surgery should commence at the site with the highest volume of residual disease. The histology of the mass diverges in different organ sites [212]. In cases of residual retroperitoneal and lung 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 [229]. When pathologic examination of the lesions from the initial side show complete necrosis, observation may be considered when there are multiple contralateral tumours for which resection may be challenging. Discordant histology between lung sites, however, may occur in up to 20% of cases and thus, patients in this situation should be closely monitored with reconsideration of surgery or biopsy if radiological features change [230, 231].

6.3.3.1 Quality and intensity of surgery

Resection of visceral structures and/or major vessels, requiring vascular reconstruction/replacement may be required to achieve radical resection and patients undergoing adjunctive complex surgery have a greater risk of complications [232, 233]. In patients with intermediate- or poor-risk and residual disease > 5 cm, the probability of vascular procedures is as high as 20% [234]. These cases must therefore be referred to specialised centres capable of interdisciplinary surgery (gastro-enteric and vascular surgery, spinal neurosurgery, thoracic surgery). Even with centralisation of treatment, the median number of RPLNDs performed per surgeon/year in the U.K. is six [235]. Nevertheless, patients treated within such centres benefit from a significant reduction in peri-operative mortality from 6% to 0.8% [236]. In addition, specialised urologic surgeons are capable of reducing the local recurrence rate from 16% to 3% with a higher rate of complete resections [237].

6.3.3.2 Salvage and desperation surgery

Surgery of resectable disease after salvage treatment remains a potentially curative option in patients with any residual mass following salvage chemotherapy. Survival after surgery and first salvage chemotherapy improved by 70% at ten years, following taxane-containing regimens [238]. Even with extensive salvage chemotherapy, surgery remains a fundamental tool to achieve durable complete remissions in up to 20% of patients [239, 240].

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 [241].

6.3.3.3 Consolidation chemotherapy after secondary surgery

After resection of necrosis or post-pubertal teratoma, no further treatment is required. With 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) [224]. Caution is required with cumulative doses of bleomycin which should not exceed 12 in total. With complete resection of active disease, comprising < 10% of the total volume of the mass, particularly in patients who initially had a good-prognosis based on IGCCCG criteria, the relapse rate is very low and adjuvant chemotherapy is not beneficial in preventing further relapse [242]. The prognosis is worse if malignant disease is present in masses resected after second- and third-line chemotherapy, although further chemotherapy is not indicated [243].

6.3.4 ***Systemic salvage treatment for relapse or refractory disease***

Cisplatin combination salvage chemotherapy will result in long-term remissions in approximately 50% of patients who relapse after first-line chemotherapy. These results are highly dependent on several prognostic factors [244]. The regimens of choice are four cycles of a three-agent regimen including cisplatin and ifosfamide plus a third drug: etoposide (VIP), paclitaxel (TIP), or potentially gemcitabine (GIP) (Table 7) [245, 246]. No RCT has compared these regimens. Due to their potential risk of lethal haematological toxicity, these regimens should be used with G-CSF support and by well-trained oncologists.

Table 7: Standard VIP, TIP and GIP salvage chemotherapy (interval 21 days)

Regimen	Chemotherapy agents	Dosage	Duration of cycles
VIP	Cisplatin* Etoposide Ifosfamide*	20 mg/m^2 75-100 mg/m^2 1.2 g/m^2	Days 1-5 Days 1-5 Days 1-5
TIP	Paclitaxel Ifosfamide* Cisplatin*	250 mg/m^2 [xx] 1.5 g/ m^2 25 mg/m^2	24 hour continuous infusion day 1 Days 2-5 Days 2-5
	Alternative schedule		
	Paclitaxel Ifosfamide* Cisplatin*	175 mg/m^2 1.2 g/m^2 20 mg/m^2	Day 1, 3 hour infusion Days 1-5 Days 1-5
GIP	Gemcitabine Ifosfamide Cisplatin	1000 mg/m^2 1200 mg/m^2 20 mg/m^2	Day 1 + 5 Days 1-5 Days 1-5

[xx] *An MRC schedule uses paclitaxel at 175 mg/m^2 in a 3 hour infusion infusion [246].*

Please refer to appendix 4 – Chemotherapeutic protocols https://uroweb.org/guidelines/testicular-cancer/publications-appendices for more detailed information.

A retrospective analysis by the International Prognostic Factors Study Group (IPFSG) evaluated the risk of relapse in patients in whom this occurred after at least three cisplatin cycles and subsequent cisplatin conventional-dose or carboplatin-based high-dose salvage chemotherapy [149]. Seven variables: histology, primary tumour location, response, progression-free interval after first-line treatment and level of AFP, β-hCG and the presence of liver, bone or brain metastasis at salvage treatment, were identified as independent prognostic variables of relapse after initial cisplatin chemotherapy [149]. Using these factors, five risk-groups: very low-risk = -1 points; low-risk = 0 points; intermediate-risk = 1-2 points; high-risk = 3-4 points; and very high-risk > 5 points; were identified with significant differences in PFS and OS. Table 9 illustrates these five risk groups and the corresponding two-year PFS and three-year OS rates [149]. Several recent trials have validated this scoring system [247-250]. As in first-line therapy, the prognostic impact of tumour marker decline applies in the salvage setting [251]. While progression to induction chemotherapy was negative for OS, prior use of paclitaxel was not significantly associated with a negative outcome [252].

A secondary analysis of the IPFSG cohort (n = 1,600 patients) showed a 10-15% improvement in OS in all prognostic subgroups when treated with high-dose salvage therapy compared to standard dose therapy. This is being evaluated in an RCT of HDCT vs. conventional dose chemotherapy in patients with first-line relapse is underway (Tiger trial). When HDCT 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 as the former is associated with less toxicity-related deaths [247]. A recent SR confirmed the superiority of using at least two high-dose cycles in the salvage setting over a single high-dose cycle [253]. It is clearly of the utmost importance that these rare patients with relapse are treated within clinical trials and at specialised centres.

Table 8: The International Prognostic Factors Study Group Score for seminoma and non-seminoma that relapse after cisplatin-based first-line chemotherapy [189]

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; CR = complete remission; PRm- = partial remission, negative markers; PRm+ = partial remission, positive markers; hCG = human chorionic gonadotrophin; LBB = liver, bone, brain metastases; PD = progressive disease; PFI = progression-free interval; SD = stable disease.

Table 9: PFS and OS estimates for all patients according to IGCCCG prognostic score for seminoma and non-seminoma that relapse after cisplatin-based first-line chemotherapy [190]

Score (n = 1,435)	**N**	**%**	**HR**	**2-years PFS (%)**	**3-year OS (%)**
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	-	-	-	-

HR = hazard ratio; PFS = progression-free survival; n = number of patients; OS = overall survival.

*6.3.5 **Second relapse***

No RCTs have been reported for patients with second relapse and conventional therapy appears to have limited effect. For patients who have received two series of conventionally dosed therapy (first line and first-salvage), HDCT with autologous stem cell support should be used although the prospect of cure is < 25% [248]. Retrospective data from Indiana University suggest that patients who completed HDCT may derive additional benefit from daily maintenance therapy with oral etoposide for three months post HDCT [254]. Prospective evaluation of this in a randomised phase II trial is ongoing.

Patients relapsing within four to eight weeks after platinum-based therapy, or who are progressing despite platinum-based therapy, as well as those relapsing shortly after HDCT, are considered as cisplatin refractory. Combinations of gemcitabine and oxaliplatin or the triple combination of gemcitabine, oxaliplatin and paclitaxel have resulted in response rates of 25-45% in this setting. Cisplatin re-challenge in association with gemcitabine and paclitaxel may be considered in patients with adequate renal function [255]. For patients with a second relapse not responding to the combination of oxaliplatin and gemcitabine or the triple combination, inclusion in clinical trials is encouraged.

Patients with a good response undergoing subsequent resection of residual tumour lesions may still have a 15-20% chance of long-term cure [239, 256].

Various targeted agents have generally failed in refractory disease, including immune checkpoint inhibitors [247-253, 257]. Trials combining PD1/PDL-1 and CTLA4 inhibitors are ongoing, however, even for those combinations early results are not encouraging.

6.3.5.1 Late relapse (more than two years after end of first-line treatment)

Late relapse is defined as recurrence more than two years after completion of successful primary treatment of metastatic TC [203, 258]. According to a pooled analysis, this occurs in 1.4% and 3.2% of seminoma and non-seminoma patients, respectively [259].

Based on a population-based study, all late-relapsing seminoma patients have viable GCT [260]. These can be treated with chemotherapy and radiotherapy [261].

In contrast, patients with late-relapsing NSGCT should undergo surgical resection when feasible, alone or in combination with chemotherapy. Some patients, including those with rapidly rising β-hCG, may benefit from induction salvage chemotherapy with subsequent reconsideration of surgery for resection of persisting residual masses [262]. In general, however, surgery represents the mainstay of treatment and it should be performed in most patients when feasible irrespective of the level of their tumour markers, in order to completely resect all viable GCT post-pubertal teratoma [261-265].

Survival strongly relates to the histology of the recurrent lesions rather than that of the initial disease. If not completely resectable, biopsies should be obtained for histological evaluation to direct salvage chemotherapy based on the tumour phenotype. Review by an experienced pathologist is critical to avoid misinterpretation of the therapeutic morphological changes that occur with the treatment of GCT [266]. If the patient responds to salvage chemotherapy, secondary surgery should then be undertaken if feasible. With 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 [267].

*6.3.6 **Treatment of brain metastases***

Brain metastases occur in the context of initial metastatic disease, systemic relapse and rarely as an isolated site of relapse. Long-term survival of patients presenting with brain metastases at diagnosis is poor (30-50%) and even poorer when a site of recurrent disease (five-year survival-rate is 2-5%) [268, 269]. A large international database comprising 523 patients reported 48% three-year OS rates in patients with brain metastases at initial diagnosis and 27% three-year OS rates for patients with brain metastases at relapse [58].

Chemotherapy as initial treatment proved effective in a first-line setting (potentially even as dose-intensified therapy upfront) with data also supporting the use of multimodal treatment particularly in relapsed disease [58]. Consolidation RT, even with total response after chemotherapy, should therefore be used in patients with brain metastases at relapse, but must be carefully discussed in a first-line setting [270]. Surgery may be considered in cases with a persistent solitary metastasis, depending on the systemic disease status, histology of the primary tumour and the location of the metastasis.

6.3.6.1 *Summary of evidence and recommendations for the treatment of metastatic testicular germ cell tumours*

Summary of evidence	LE
In the NSGCT good-prognosis-risk group (IGCCG), BEP x 3 is superior to other chemotherapy regimens. Toxicity is lower when treatment is delivered in five-day regimes rather than three-day regimes.	1b
In the NSGCT intermediate-prognosis-risk group (IGCCCG) BEP x 4 is the standard treatment of choice with a five-year survival of 89% in contemporary series.	1b
In pathological stage II NSGCT disease, RPLND performed in specialised centres without adjuvant chemotherapy results in 73-81% of long-lasting remissions.	2b
In patients with a poor-prognosis metastatic NSGCT (defined by IGCCCG), treatment with BEP x 4, results in a five-year PFS of 67%. There is no advantage in OS for high-dose chemotherapy.	1b
Patients with a poor-prognosis metastatic NSGCT and early unfavourable tumour marker decline may benefit from intensification of treatment with dose-dense chemotherapy, with improvement of PFS despite no benefit being observed for OS.	1b
Following first-line BEP chemotherapy, 6-10% of NSGCT residual masses contain active cancer, 50% have post-pubertal teratoma, and 40% comprise of necrotic-fibrotic tissue only. Figures regarding persistence of residual active are slightly lower in post chemotherapy residual masses < 1 cm. Currently there is no accurate prognostication method of histology.	2b
In CS IIA/B seminoma radiotherapy and chemotherapy treatment show similar effectiveness, with a non-significant trend towards greater efficacy of chemotherapy in CS IIB. However, risk of second malignancies and cardiovascular events is higher after radiotherapy.	2a
In metastatic seminoma stage > IIC, primary chemotherapy with BEP, tailored to the IGCCCG risk group, has proven superior to Carboplatin based chemotherapy.	1b
Fluorodeoxyglucose-positron emission tomography has a high NPV in patients with post-chemotherapy seminoma residual masses (> 3 cm) when performed more than two months after chemotherapy.	2b

Recommendations	Strength rating
Treat low-volume non-seminomatous germ cell tumour (NSGCT) stage IIA/B with elevated markers like metastatic good- or intermediate-prognosis risk group IGCCCG with three or four cycles of cisplatin, etoposide, bleomycin (BEP).	Strong
Nerve-sparing retroperitoneal lymph node dissection when performed by an experienced surgeon in a specialised centre is the recommended initial treatment in clinical stage (CS) IIA NSGCT disease without elevated tumour markers.	Weak
Repeat staging after six weeks before making a final decision on further management should be considered in patients with small volume (CS IIA < 2 cm) marker-negative NSGCT.	Weak
Treat metastatic NSGCT (stage > IIC) with an intermediate prognosis with four cycles of standard BEP.	Strong
Treat metastatic NSGCT with a poor prognosis and favourable marker decline with four cycles of BEP.	Strong
Assess tumour marker decline after one cycle of standard chemotherapy in metastatic NSGCT with a poor-prognosis. With unfavourable decline, consider chemotherapy intensification.	Weak
Perform surgical resection of visible (> 1 cm in longest diameter) residual masses after chemotherapy for NSGCT when serum levels of tumour markers are normal or normalising.	Strong
Offer cisplatin chemotherapy according to IGCCCG prognosis groups, or alternatively radiotherapy to seminoma patients with stage II A/B and, inform the patient of potential long-term side effects of both treatment options.	Weak
Treat seminoma stage IIC and higher, with primary chemotherapy according to IGCCCG classification (BEP x 3 in good-prognosis and BEP x 4 in intermediate prognosis).	Strong

7. FOLLOW-UP AFTER CURATIVE THERAPY

7.1 Minimal recommendations for follow-up

Based on different risks of relapse depending on diagnosis and initial treatment, three major follow-up groups can be defined:

1. patients with seminoma stage I;
2. patients with non-seminoma stage I on active surveillance;
3. all patients having received either adjuvant treatment or curative chemotherapy for good- and intermediate-prognosis metastatic disease (according to the IGCCCG) achieving a complete remission with, or without, surgery (for seminoma this includes residual lesions < 3 cm, or residual lesions > 3 cm that are FDG-PET-negative).

It is important to note that patients not achieving a complete remission or presenting with poor-prognosis disease should be followed up individually by specialised centres. Tables 10-12 show the minimal recommendations for follow-up of the three different groups based on recommendations developed at a European Society for Medical Oncology (ESMO) consensus conference [271].

Both MRI and CT can be used to evaluate the retroperitoneum, pelvis and inguinal regions for sites of metastatic disease from GCT [272, 273]. Magnetic resonance imaging benefits from an absence of ionising radiation but is more time consuming and less readily available than CT [274]. Given the frequency of follow-up, over a number of years some studies have estimated a risk of up to 1 in 300 of second malignancy related to CT imaging follow-up alone [275], although more recent dose saving protocols and limitations on field of view will have mitigated this somewhat. Nevertheless, this risk could be excluded by the use of MRI for follow-up.

Both MRI and CT rely predominantly on size cut-offs for evaluation given the excellent spatial resolution of both modalities, with morphological assessment for features such as necrosis and irregular shape an adjunct. Sensitivity and specificity vary according to the size cut-off used [272]. However, studies have shown comparable excellent results between MRI and CT with up to 98% sensitivity on MRI for the detection of retroperitoneal nodal metastases in GCT [276]. It has, however, been demonstrated that reader experience is important when interpreting images [277]. In the setting of GCT, one study demonstrated decreased sensitivity for detection of retroperitoneal nodal disease on MRI when reported by a trainee radiologist with sensitivity of detection of 80% [275]. However, experienced radiologists in the same study again achieved sensitivity for detection of nodal disease of 97% with good interobserver agreement. It was therefore suggested that if MRI is to be used instead of CT for follow-up this be done in centres/units with oncological radiologists who routinely report MRI and CT in patients with GCT rather than general radiologists who may only occasionally see such imaging. Consequently, MRI of the abdomen can be used as an alternative to CECT in experienced centres [278].

The diagnostic accuracy of FDG-PET-CT is best described and therefore recommended in seminoma patients with post-chemotherapy residual masses > 3 cm in largest diameter as outlined in section 6.3.2.1. This should be performed at least 2 months after completion of chemotherapy as earlier scans may be misleading due to inflammation. The changes related to tumour necrosis. The use of FDG-PET-CT is not currently recommended during surveillance. Retrospective analyses have indicated a high diagnostic accuracy for staging and follow-up in patients with CS 1 during surveillance or for determining the stage in more advanced disease [279]. However, to minimise radiation exposure and considering the supporting data for the use of MRI [273], the panel currently do not recommend the use of FDG-PET-CT during surveillance.

Serum tumour markers are the least invasive and most accessible follow-up investigations. The established serum tumour markers, such as AFP, β-hCG, and LDH, may yield false positive results, so their levels should be correlated with imaging findings or repeated in serial measurements [280]. Serum tumour markers can detect microscopic disease that is not yet visible on cross-sectional imaging in a small proportion of patients, and therefore, they should be measured at the recommended prescribed intervals [281].

MiR-371a-3p has a high diagnostic accuracy for detecting all histologies of GCT except teratoma and has potential to detect disease recurrence earlier than AFP, β-hCG, LDH, or cross-sectional imaging [282]. However, before this promising test can be recommended in routine practice, a validated assay and cut-off definitions in prospective cohorts are required to mitigate the risk of false positive findings, unnecessary restaging, anxiety, or over-treatment.

Regarding the use of US examination of the contralateral testis, the majority of the consensus meeting participants did not support repeat US investigation, either with negative biopsy or if no contralateral biopsy has been performed [271].

A very late relapse (VLR) after five years is a rare event occurring in approximately 0.5% of patients based on a population-based analysis [260]. The aim of follow-up beyond five years therefore shifts to detection of late side effects of treatment and imaging tests are not routinely recommended.

Most patients with VLR are diagnosed due to symptoms, although in up to 50% elevated tumour markers are present in NSGCTs [260, 283]. Patient education regarding relapse symptoms and clinician awareness are important elements of survivorship management. Early use of imaging and tumour markers with suspicion of relapse is encouraged.

Table 10: Recommended minimal follow-up for seminoma clinical stage I on active surveillance or after adjuvant treatment (carboplatin or radiotherapy)

Modality	Year 1	Year 2	Year 3	Years 4 & 5	After 5 years
Tumour markers ± doctor visit	2 times	2 times	2 times	Once	Further management according to survivorship care plan
Chest X-ray	-	-	-	-	
Abdominopelvic magnetic resonance imaging (MRI)/ computed tomography (CT)	2 times	2 times	Once at 36 months	Once at 60 months	

Table 11: Recommended minimal follow-up for non-seminoma clinical stage I on active surveillance

Modality	Year 1	Year 2	Year 3	Year 4 & 5	After 5 years
Tumour markers ± doctor visit	4 times*	4 times	2 times	1-2 times	Further management according to survivorship care plan
Chest X-ray	2 times	2 times	Once, in case of LVI+	At 60 months if LVI+	
Abdominopelvic magnetic resonance imaging (MRI)/ computed tomography (CT)	2 times	At 24 months**	Once at 36 months***	Once at 60 months***	

** In case of high-risk (LVI+) a minority of the consensus group members recommended six times.*

*** In case of high-risk (LVI+) a majority of the consensus group members recommended an additional CT at eighteen months.*

**** Recommended by 50% of the consensus group members.*

LVI+ = Lymphovascular invasion present

Table 12: Recommended minimal follow-up after adjuvant treatment or complete remission for advanced disease (excluded: poor-prognosis and no remission)

Modality	Year 1	Year 2	Year 3	Year 4 & 5	After 5 years
Tumour markers ± doctor visit	4 times	4 times	2 times	2 times	Further management according to survivorship care plan**
Chest X-ray	1-2 times	Once	Once	Once	
Abdominopelvic magnetic resonance imaging (MRI)/ computed tomography (CT)	1-2 times	At 24 months	Once at 36 months	Once at 60 months	
Thorax CT	1-2 times*	At 24 months*	Once at 60 months*	Once at 60 months*	

** In conjunction with abdominopelvic MRI/CT in case of pulmonary metastases at diagnosis.*

*** In case of teratoma in resected residual disease: the patient should remain with the uro-oncologist.*

7.2 Quality of life and long-term toxicities after cure of testicular cancer

The vast majority of patients will be cured with five-year relative survival rates of approximately 95% in Western Europe. Testicular cancer patients are usually between 18-40 years of age at diagnosis and life expectancy after cure extends over several decades [284]. Patients should be informed before treatment of common long-term toxicities, which are avoided or minimised by adherence to international guidelines.

During follow-up, patients should be screened and treated for known risk factors such as hypertension, hyperlipidaemia, and testosterone deficiency. Adverse health outcomes (AHOs) are more commonly found in TC patients who received chemotherapy than those cured by surgery alone. Further, modifiable risk factors do contribute to AHOs like hypertension and noise exposure to hearing impairment or smoking to Raynaud phenomenon [285]. Therefore, a healthy lifestyle should be promoted during the follow-up consultations. Adverse health outcomes are associated with unemployment, which is found clearly increased in TC survivors (TCSs) as compared to a male normative population [286]. When follow-up by the TC clinician is terminated, a written cancer survivorship plan addressing late toxic effects, lifestyle recommendations, recurrence risk, and cancer-specific follow-up may be helpful [203, 287].

*For more information regarding long term toxicities and quality of life issues, please see appendix 3, available online https://uroweb.org/guidelines/testicular-cancer/publications-appendices

8. RARE ADULT PARA- AND TESTICULAR TUMOURS

Less than 5% of testicular cancers are unrelated to GCNIS and lack 12p alterations [288, 289]. These tumours are rare with available literature based on case reports and small retrospective series. Given the rarity of non-germ cell para-/testicular cancers, referral of these cases to specialist units for multidisciplinary discussion including central image and pathology review is highly recommended. As a result of publication bias related to these types of study, the risk of metastatic disease may be less than that reported in the literature.

8.1 Classification

These testicular tumours have a similar presentation as TC and are only identified after histopathologic examination. They are classified according to the WHO Classification of Tumours of the Urinary System and Male Genital Organs [290].

8.2 Spermatocytic Tumours

Spermatocytic tumours are GCTs unrelated to GCNIS. They may show a unique amplification of chromosome 9 corresponding to the DMRT1 gene and are never associated with other forms of germ cell tumours [290].

Spermatocytic tumours are rare, occur exclusively in the testis and do not normally show elevated tumour markers [290]. Previously named “spermatocytic seminomas” they have been recently reclassified as spermatocytic tumours [290]. As those tumours cannot be differentiated from seminoma GCT by FSE, radical orchiectomy is the standard treatment option. Outcomes after testis-sparing surgery or adjuvant treatment is unknown and therefore not recommended [291]. Metastatic disease is very rare, usually associated with ‘sarcomatoid change’ and typically presents at or soon after initial diagnosis with limited survival [291].

8.3 Sex cord-stromal tumours

Sex cord–stromal tumours are relatively uncommon but represent the second largest group of primary testicular tumours after GCT’s [292]. As a small subset of these tumours are clinically malignant, a thorough evaluation of those morphological features associated with malignancy should be performed to guide management. Two or more of the following features are associated with malignant potential: size > 5 cm, infiltrative borders, cytological atypia, three or more mitotic figures per ten high-power fields, vascular invasion and necrosis [292].

8.3.1 Leydig cell tumours

Leydig cell tumours comprise about 4% of adult testicular tumours [293]. These mainly present as localised tumours with metastases occurring in only 2.5% [294]. They may present with hormonal manifestations, including gynaecomastia and more rarely are accompanied by Cushing's Syndrome [389]. With testis-sparing surgery a local recurrence rate of 7% has been reported although no adjuvant treatment options can be recommended [295]. Several risk factors for metastatic disease have been proposed which may guide image-guided follow-up intensity [295]. Survival of men with metastatic disease is poor but occasional responses to surgical resection, if feasible, and to a lesser extent systemic treatment have been reported [295].

8.3.2 Sertoli cell tumours

Sertoli cell tumours account for approximately 1% of testicular neoplasms [292]. The risk of metastases is unclear. With testis sparing surgery a local recurrence rate of < 1% has been reported although no adjuvant treatment options can be recommended [296]. Several risk factors for metastatic disease have been proposed which may guide image guided follow-up intensity [296]. Survival of men with metastatic disease is poor although response to surgery has been occasionally reported [296].

8.3.3 Granulosa cell tumour

Granulosa cell tumours, which include adult and juvenile variants, are extremely rare and metastatic potential is unclear [292]. With testis sparing surgery a local recurrence rate of 5% has been reported although no adjuvant treatment options can be recommended [297]. Whereas metastatic disease has never been reported in juvenile granulosa cell tumours, men with adult type may occasionally present with metastatic disease [297]. Survival of men with metastatic disease is poor although rare instances of response to surgical or systemic treatment has been reported [297].

8.3.4 Thecoma/fibroma group of tumours

These tumours derive from the testicular parenchymal stroma or from the tunica albuginea. They seem to be uniformly benign [292, 298].

8.3.5 Paratesticular tumours of the epididymis or spermatic cord

The majority of epididymal masses are benign cystic or inflammatory conditions. Solid epididymal tumours are rare and comprise numerous benign and neoplastic lesions. In the only population-based analyses [299], the majority of neoplastic lesions of the epididymis or spermatic cord were sarcomas, metastases from other organs or primary adenocarcinomas similar to proportions reported in institutional studies [300, 301]. Benign lesions, which may comprise the majority in clinical practice include lipomas, adenomatoid tumours leiomyomas and papillary cystadenomas.

Robust criteria to differentiate between neoplastic benign lesions have not been defined although ultrasonography with or without fine needle aspiration [302] MRI [53, 303] or surgical exploration with FSE or histopathological confirmation can be considered. No clear recommendation can be provided regarding surgical approach, extent of resection and neo- or adjuvant treatment can be given.

8.4 Mesothelioma of the tunica vaginalis testis

Mesothelioma of the tunica vaginalis testis is a rare but aggressive disease [304]. Beside older age, larger tumour size, presence of necrosis, angiolymphatic invasion or a high mitotic index the only modifiable risk factors represents local recurrence. Therefore, aggressive local treatment with hemiscrotectomy is recommended. No clear recommendation can be given regarding adjuvant treatment. In case of metastatic disease, the median overall survival is a few months only and multimodal treatment could be considered.

8.5 Follow-up of rare adult para- and testicular cancers

After local surgical treatment is completed, attention turns to follow-up strategies with the aims of detecting recurrence or secondary cancers at a stage when further curative procedures are possible whilst minimising the burden of follow-up and the potential for over-treatment and concomitant treatment toxicity. Data for rare para- and testicular cancers are limited but recommended follow-up schedules based on published case series have been suggested [305].

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10. 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 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.

11. CITATION INFORMATION

The format in which to cite the EAU Guidelines will vary depending on the style guide of the journal in which the citation appears. Accordingly, the number of authors or whether, for instance, to include the publisher, location, or an ISBN number may vary.

The compilation of the complete Guidelines should be referenced as:
EAU Guidelines. Edn. presented at the EAU Annual Congress Paris 2024. ISBN 978-94-92671-23-3.

If a publisher and/or location is required, include:
EAU Guidelines Office, Arnhem, the Netherlands. http://uroweb.org/guidelines/compilations-of-all-guidelines/

References to individual guidelines should be structured in the following way:
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EAU Guidelines on

Primary Urethral Carcinoma

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European Association of Urology

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1. INTRODUCTION

1.1 Aims and scope

This overview represents the updated European Association of Urology (EAU) Guidelines for primary urethral carcinoma. The aim is to provide practical recommendations on the clinical management of Primary Urethral Carcinoma with a focus on clinical presentation. When the first carcinoma in the urinary tract is detected in the urethra, this is defined as primary urethral carcinoma, in contrast to secondary urethral carcinoma, which presents as recurrent carcinoma in the urethra after prior diagnosis and treatment of carcinoma elsewhere in the urinary tract. Most often, secondary urethral carcinoma is reported after radical cystectomy for bladder cancer [1, 2] (see Chapter 7.3 of the European Association of Urology [EAU] Guidelines on Muscle-invasive and Metastatic Bladder Cancer [MIBC]) [2].

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

1.2 Panel composition

The EAU Guidelines Panel on MIBC is responsible for this publication. This is an international multidisciplinary group of clinicians, including urologists, oncologists, a pathologist, a radiotherapist and a radiologist. Members of this panel have been selected based on their expertise to represent the professionals treating patients suspected of suffering from urethral carcinoma. In the course of 2021 two patient representative have formally joined the MIBC Guidelines Panel. 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/primary-urethral-carcinoma/.

1.3 Available publications

A quick reference document (Pocket guidelines) is available in print, presenting the main findings of the Primary Urethral Carcinoma Guidelines. This is an abridged version which may require consultation together with the full text version. The most recent scientific summary was published in 2020 [3].

1.4 Publication history & summary of changes

The Primary Urethral Carcinoma Guidelines were first published in 2013. This is the tenth update of this document.

1.4.1 Summary of changes

The literature for the complete document has been assessed and updated for the 2024 print, resulting in a text update in section 3.3 on histopathology and genomic profiling.

2. METHODS

2.1 Data identification

For the 2023 Primary Urethral Carcinoma Guidelines, new and relevant evidence has been identified, collated, and appraised through a structured assessment of the literature. An updated systematic literature search was performed to identify studies reporting data on urethral malignancies since the prior search, covering a time frame between August 9th 2022 and May 1st 2023. Databases searched included Ovid (Medline), EMBASE and the Cochrane Central Register of Controlled Trials and Cochrane Database of Systematic Reviews. A total of 68 unique records were identified, retrieved, and screened for relevance. Only one reference was updated in this 2023 publication. A detailed search strategy is available online: https://uroweb.org/guidelines/primary- urethral-carcinoma/publications-appendices.

Recommendation within the Guidelines are developed by the panels to prioritise clinically important care decisions. The strength of each recommendation is determined by the balance between desirable and undesirable consequences of alternative management strategies, the quality of the evidence (including certainty of estimates), and the nature and variability of patient values and preferences. This decision process, which can be reviewed in the strength rating forms which accompany each guideline statement, addresses a number of key elements:

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

Strong recommendations typically indicate a high degree of evidence quality and / or a favourable balance of benefit to harm and patient preference. Weak recommendations typically indicate availability of lower quality evidence, and/ or equivocal balance between benefit and harm, and uncertainty or variability of patient preference [5]. The strength rating forms will be available online.

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 peer-reviewed prior to publication in 2021.

3. EPIDEMIOLOGY, AETIOLOGY AND PATHOLOGY

3.1 Epidemiology

Primary urethral carcinoma is considered a rare cancer, accounting for < 1% of all genitourinary malignancies [6] (ICD-O3 topography code: C68.0) [7]. In 2013, the prevalence of urethral carcinoma in the 28 European Union countries was 3,986 cases with an estimated annual incidence of 1,504 new cases, with a male/female prevalence of 2.9: 1 [8]. Likewise, in an updated analysis of the Surveillance, Epidemiology and End Results (SEER) database (2004–2016), the incidence of primary urethral carcinoma 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) [9]. After matching for tumour and patient characteristics, women present with higher disease stage and exhibited higher cancer-specific mortality (CSM) [10].

3.2 Aetiology

For male primary urethral carcinoma, various predisposing factors have been reported, including urethral strictures [11, 12], chronic irritation after intermittent catheterisation/urethroplasty [13-15], external beam irradiation therapy (EBRT) [16], radioactive seed implantation [17], chronic urethral inflammation/urethritis following sexually transmitted diseases (i.e., condylomata associated with human papilloma virus 16) [18, 19] and lichen sclerosis [12]. In female urethral carcinoma, urethral diverticula [20-22] and recurrent urinary tract infections [23] have been associated with primary urethral carcinoma. Mid-urethral sling meshes have not been associated with an increased risk of primary urethral carcinoma [24]. Clear-cell adenocarcinoma (AC) may also have a congenital origin [25, 26].

3.3 Histopathology and genomic profiling

Both the Surveillance of Rare Cancers in Europe (RARECARE) project and SEER database have reported that urothelial carcinoma (UC) of the urethra is the predominant histological type of primary urethral cancer (54–65%), followed by squamous cell carcinoma (SCC) (16–22%) and AC (10–16%) [8, 27].

A SEER analysis of 2,065 men with primary urethral carcinoma (mean age 73 years) found that UC was most common (78%), and SCC (12%) and AC (5%) were significantly less frequent [28]. In women, AC is the more frequent histology (38–46.7%) followed by SCC (25.4–28%), UC (24.9–28%) and other histological entities (6%) [29, 30]. Primary UC with unconventional histological subtypes are very rare and exhibit a dismal prognosis [31]. An analysis of the SEER database from 2004 to 2016 identified 165 cases of Primary UC with unconventional histological subtypes, 70.3% of which were in women, and reported that Mullerian-type tumor is the most frequent unconventional histology of urethral cancer, followed by melanocytic-type histology [31].

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4. STAGING AND CLASSIFICATION SYSTEMS

4.1 Tumour, Node, Metastasis (UICC/TNM) staging system

In men and women, urethral carcinoma is classified according to the 8th edition of the TNM classification [7] (Table 4.1). It should be noted that there is a separate TNM staging system for prostatic UC [7]. Of note, for cancers occurring in the urethral diverticulum, stage T2 is not applicable as urethral diverticula are lacking periurethral muscle [32].

Table 4.1: TNM classification (8th edition) for urethral carcinoma [7]

T - Primary Tumour	
TX	Primary tumour cannot be assessed
T0	No evidence of primary tumour
Urethra (male and female)	
Ta	Non-invasive papillary, polypoid, or verrucous carcinoma
Tis	Carcinoma *in situ*
T1	Tumour invades subepithelial connective tissue
T2	Tumour invades any of the following: corpus spongiosum, prostate, periurethral muscle
T3	Tumour invades any of the following: corpus cavernosum, beyond prostatic capsule, anterior vagina, bladder neck (extraprostatic extension)
T4	Tumour invades other adjacent organs (invasion of the bladder)
Urothelial (transitional cell) carcinoma of the prostate	
Tis pu	Carcinoma *in situ,* involvement of prostatic urethra
Tis pd	Carcinoma *in situ,* involvement of prostatic ducts
T1	Tumour invades subepithelial connective tissue (for tumours involving prostatic urethra only)
T2	Tumour invades any of the following: prostatic stroma, corpus spongiosum, periurethral muscle
T3	Tumour invades any of the following: corpus cavernosum, beyond prostatic capsule, bladder neck (extraprostatic extension)
T4	Tumour invades other adjacent organs (invasion of the bladder or rectum)
N - Regional Lymph Nodes	
NX	Regional lymph nodes cannot be assessed
N0	No regional lymph node metastasis
N1	Metastasis in a single lymph node
N2	Metastasis in multiple lymph nodes
M - Distant Metastasis	
M0	No distant metastasis
M1	Distant metastasis

4.2 Tumour grade

Non-urothelial urethral carcinoma is graded by a trinomial system that differentiates between well-differentiated (G1), moderately-differentiated (G2), and poorly-differentiated tumours (G3). In primary urothelial carcinoma histological subtypes are extremely rare. Table 4.2 lists the different grading systems according to the WHO 2022 system [33].

Table 4.2: Histopathological grading of urothelial and non-urothelial primary urethral carcinoma [33]

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

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

4.3 Handling of tumour specimens

Specimen handling should follow the general rules as published by the International Collaboration on Cancer Reporting [34].

Table 4.3: Required and recommended elements for pathology reporting of carcinoma of the urethra in urethrectomy specimens [7, 34]

Required		Recommended	
Operative procedure		Clinical information	Previous history of urinary tract disease or distant metastasis
Additional specimens submitted			Previous therapy
Maximum tumour dimension	Cannot be assessed		Other clinical information
	No macroscopically visible tumour	Tumour focality	
	Maximum tumour dimension (largest tumour)	Other tumour dimensions (than maximum dimension) of the largest tumour	
Macroscopic tumour site		Block identification key	
Macroscopic extent of invasion		Associated epithelial lesions	
Histological tumour type	Histological subtype/ variant (urothelial carcinoma)	Extranodal spread for involved regional lymph node(s)	
Non-invasive carcinoma		Coexistent pathology	
Histological tumour grade		Ancillary studies	
Microscopic extent of invasion			
Lymphovascular invasion			
Margin status			
Regional lymph node status	No regional lymph nodes submitted		

4.4 Guideline for staging and classification systems

Recommendation	Strength rating
Use the 2017 TNM classification and 2022 WHO grading system for pathological staging and grading of primary urethral carcinoma.	Strong

5. DIAGNOSTIC EVALUATION AND STAGING

5.1 History

When becoming clinically apparent, most patients (45–57%) with primary urethral carcinoma present with symptoms associated with locally-advanced disease (T3/T4) [35]. 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 extra-urethral mass (52%), bladder outlet obstruction (48%), pelvic pain (33%), urethrocutaneous fistula (10%), abscess formation (5%) or dyspareunia [35].

5.2 Clinical examination

In men, physical examination should comprise palpation of the external genitalia for suspicious indurations or masses and digital rectal examination [36]. In women, further pelvic examination and palpation of the urethra should be performed. In addition, bimanual examination, when necessary under general anaesthesia, should be performed for local clinical staging and to assess whether colorectal or gynaecological malignancies are present.

Bilateral inguinal palpation should be done to assess the presence of enlarged LNs, describing location, size, and mobility [37].

5.3 Urinary cytology

Urinary cytology is part of the standard work-up of a patient with suspected primary urethral carcinoma. Reporting of urinary cytology findings should follow the Paris system [38]. However, the role of urinary cytology in primary urethral carcinoma is limited since its sensitivity ranges between 55% and 59% [39]. 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 [39].

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 [36]. Cystoscopic examination is necessary to exclude the presence of concomitant bladder tumours [40].

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 [41]. In patients with suspected UC of the prostatic urethra or ducts, resectoscope loop biopsy of the prostatic urethra (between the five and seven o'clock position from the bladder neck and distally around the area of the verumontanum) can contribute to an improved detection rate [42].

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. To obtain all relevant information, the collection, handling, and evaluation of biopsy specimen should follow the recommendations provided by the International Collaboration on Cancer Reporting (see Table 4.3) [34].

5.5 Imaging for diagnosis and staging

Radiological imaging of urethral carcinoma aims to assess local staging and to detect lymphatic and distant metastatic spread. In a recent multicentre study, the accuracy of cross-sectional imaging for clinical tumour and nodal staging predicting final pathological staging was found to be 72.9% and 70.6%, respectively [43]. Imaging work-up should include computed tomography (CT) of the chest, abdomen and pelvis for staging, including CT urography for urothelial evaluation. Magnetic resonance imaging (MRI) can be used to evaluate tumour location and size, as well as local tumour extent and presence of regional LN metastases, focusing in particular on inguinal and pelvic LNs [44-48].

For local staging, there is evidence that MRI is an accurate tool for monitoring tumour response to neoadjuvant chemoradiotherapy and evaluating the extent of local disease prior to exenterative surgery [49].

^{18}F-Fluorodeoxglucose positron emission tomography/MRI has shown to improve the diagnostic evaluation in patients with metastatic disease [50].

5.6 Regional lymph nodes

In urethral carcinoma enlarged LNs often represent metastatic disease (~84% of patients) [51-53], which is in contrast to penile cancer where this is the case in ~41% of patients [54]. In men, lymphatics from the anterior urethra drain into the superficial- and deep inguinal LNs and, subsequently, to the pelvic (external, obturator and internal iliac) LNs. Conversely, lymphatic vessels of the posterior urethra drain into the pelvic LNs. In women, the lymph of the proximal third drains into the pelvic LN chains, whereas the distal two-thirds initially drain into the superficial- and deep inguinal nodes [55, 56].

5.7 Summary of evidence and guidelines for diagnostic evaluation and staging

Summary of evidence	LE
Patients with clinically enlarged inguinal or pelvic LNs often exhibit pathological LN metastasis.	3

Recommendations	Strength rating
Use urethrocystoscopy with biopsy and urinary cytology to diagnose urethral carcinoma.	Strong
Assess the presence of distant metastases by computed tomography of the thorax and abdomen/pelvis.	Strong
Use pelvic magnetic resonance imaging to assess the local extent of urethral tumour and regional lymph node enlargement.	Strong

6. PROGNOSIS

6.1 Long-term survival after primary urethral carcinoma

According to the RARECARE project, the one- and 5-year relative overall survival (OS) rates in patients with urethral carcinoma in Europe are 71% and 54%, respectively [8]. Based on longer follow-up, an analysis of the SEER database, comparing prognostic factors in rare pathological types of primary urethral carcinoma (n = 257) and common pathological groups (n = 2,651), reported 10-year OS rates of 42.4% and 31.9%, respectively [57]. Cancer-specific survival (CSS) rates at five and ten years were 68% and 60%, respectively [58]. Age (> 60 years), race (others vs. whites), T-stage (T3/T4 vs. Ta–T2) and M-stage (M1 vs. M0) were independent prognostic risk factors for OS and CSS in rare pathological variants [57].

6.2 Predictors of survival in primary urethral carcinoma

Previous series reported no substantial difference in 5-year OS rates between the sexes [8, 30, 59], whereas in a recent SEER analysis female patients showed higher stage disease and 5-year CSM despite higher use of multimodal therapy [10, 60]. Prognostic factors of worse survival in patients with primary urethral carcinoma are:

- advanced age (> 65 years) and black race [8, 30, 60, 61];
- higher stage, grade, nodal involvement [52, 62] and metastasis [28];
- increased tumour size and proximal tumour location [28];
- underlying (non-urothelial or unconventional) histology [8, 28, 31, 61-64];
- presence of concomitant bladder cancer [40];
- extent of surgical treatment and treatment modality [28, 61, 62];
- treatment in academic centres [65];
- location of recurrence (urethral vs. non-urethral) [66].

Some limitations have to be considered when interpreting these results as the number of patients included in most studies were low [63].

6.3 Summary of evidence for prognosis

Summary of evidence	LE
Prognostic factors for survival in primary urethral carcinoma are: age, gender, 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
In locally-advanced urothelial- and SCC of the urethra, treatment in academic centres improves OS.	3

7. DISEASE MANAGEMENT

7.1 Treatment of primary urethral carcinoma in males

Previously, treatment of male distal urethral carcinoma followed the procedure for penile cancer, with surgical excision of the primary lesion with a wide safety margin [36]. Distal urethral tumours exhibit significantly improved survival rates compared with proximal tumours [67]. Therefore, in the treatment of distal urethral carcinoma the focus of clinicians has shifted towards improving functional outcomes and quality of life (QoL), 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 distal urethral carcinoma treated with well-defined penile-preserving surgery and additional iliac/inguinal lymphadenectomy (LND) for clinically suspected LN disease [68]. Similar results for the feasibility of penile-preserving surgery have also been reported in recent series [69, 70]. However, a series on patients treated with penile-preserving surgery for distal urethral carcinoma reported a higher risk of progression in patients with positive proximal margins, which was also more frequently observed in cases with lymphovascular and peri-neural invasion of the primary tumour [71].

7.1.1 Summary of evidence and guidelines for the treatment of primary urethral carcinoma in males

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

Recommendations	Strength rating
Offer distal urethrectomy as an alternative to penile amputation in localised distal urethral tumours, if negative surgical margins can be achieved intra-operatively.	Weak
Ensure complete circumferential assessment of the proximal urethral margin if penile preserving surgery is intended.	Strong

7.2 Treatment of localised primary urethral carcinoma in females

7.2.1 Urethrectomy and urethra-sparing surgery

In women with localised urethral carcinoma, to provide the highest chance of local cure, primary radical urethrectomy should include removal of all the peri-urethral tissue from the bulbocavernosus muscle bilaterally and distally, with a cylinder of all adjacent soft tissue up to the pubic symphysis and bladder neck. Bladder neck closure and appendicovesicostomy for primary distal urethral lesions has been shown to provide satisfactory functional results [37].

Previous series have reported outcomes in women with mainly distal urethral tumours undergoing primary treatment with urethra-sparing surgery, with or without additional radiotherapy (RT) compared to primary urethrectomy with the aim of maintaining integrity and function of the lower urinary tract [72, 73]. In longer-term series with a median follow-up of 153–175 months, local recurrence rates in women undergoing partial urethrectomy with intra-operative frozen section analysis were 22–60%, and distal sleeve resection of > 2 cm resulted in secondary urinary incontinence in 42% of patients who subsequently required additional reconstructive surgery [72, 73].

Ablative surgical techniques, i.e., transurethral resection (TUR) or laser, used for small distal urethral tumours, have also resulted in considerable local failure rates of 16%, with a CSS rate of 50%. This emphasises the critical role of local tumour control in women with distal urethral carcinoma to prevent local and systemic progression [72].

*7.2.2 **Radiotherapy***

In women, RT was investigated in several older series with a medium follow up of 91–105 months [74]. 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% [74]. Most local failures (95%) occurred within the first two years after primary treatment [74]. The extent of urethral tumour involvement was found to be the only parameter independently associated with local tumour control but the type of RT (EBRT vs. interstitial brachytherapy) was not [74]. In one study, the addition of brachytherapy to EBRT reduced the risk of local recurrence by a factor of 4.2 [75]. Of note, pelvic toxicity in those achieving local control was considerable (49%), including urethral stenosis, fistula, necrosis, cystitis and/ or haemorrhage, with 30% of the reported complications graded as severe [74].

*7.2.3 **Summary of evidence and guidelines for the treatment of localised primary urethral carcinoma in females***

Summary of evidence	LE
In females with distal urethral tumours, urethra-sparing surgery and local RT represent alternatives to primary urethrectomy but are associated with increased risk of tumour recurrence and local toxicity.	3

Recommendations	Strength rating
Offer urethra-sparing surgery, as an alternative to primary urethrectomy, to females with distal urethral tumours, if negative surgical margins can be achieved intra-operatively.	Weak
Offer local radiotherapy, as an alternative to urethral surgery, to females with localised urethral tumours but discuss local toxicity.	Weak

7.3 Multimodal treatment in locally-advanced urethral carcinoma in both males and females

*7.3.1 **Introduction***

Multimodal therapy in primary urethral carcinoma consists of definitive surgery plus chemotherapy with additional RT [76]. Multimodal therapy was often underutilised as shown by Cahn and colleagues in locally-advanced disease (only 16%) notwithstanding promising results [76-79]. In a recent study monotherapy was associated with decreased local recurrence-free survival after adjusting for stage, histology, sex, and year of treatment ($p = 0.017$). Its use has decreased over time [80]. Treatment in academic centres was reported to result in higher utilisation of neoadjuvant- and multimodal treatment and improved OS in patients with locally-advanced urothelial- and SCC primary urethral carcinoma [65].

*7.3.2 **Preoperative cisplatin-based chemotherapy***

Retrospective studies reported that modern cisplatin-based combination chemotherapy regimens can be effective in advanced primary urethral carcinoma providing prolonged survival even in LN-positive disease. Moreover, they emphasised the critical role of surgery after chemotherapy to achieve long-term survival in patients with locally-advanced urethral carcinoma. In a study using the National Cancer Database in men with primary urothelial carcinoma, NAC was reported to decrease the risk of all-cause mortality, while AC was not associated with an OS benefit, as compared to no chemotherapy in men, with primary urothelial carcinoma neoadjuvant chemotherapy (NAC) was reported to exhibit improved OS compared with adjuvant chemotherapy [81].

In a series of 124 patients, 39 (31%) were treated with peri-operative platinum-based chemotherapy for advanced primary urethral carcinoma (twelve patients received NAC, six received neoadjuvant chemoradiotherapy and 21 adjuvant chemotherapy). Patients who received NAC or chemoradiotherapy for locally-advanced primary urethral carcinoma (> cT3 and/or cN+) appeared to demonstrate improved survival compared to those who underwent upfront surgery with or without adjuvant chemotherapy [82]. Another retrospective series including 44 patients with advanced primary urethral carcinoma, reported outcomes on 21 patients who had preoperatively received cisplatin-based combination chemotherapy according to the underlying histologic subtype. The overall response rate for the various regimens was 72% and the median OS 32 months [51].

7.3.3 Chemoradiotherapy in locally-advanced squamous cell carcinoma of the urethra

The clinical feasibility of local RT with concurrent chemotherapy as an alternative to surgery in locally-advanced SCC has been reported in several series. This approach offers a potential for genital preservation [83-87]. The largest, and recently updated, retrospective 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 clinical response was observed in ~80% of patients. The 5-year OS 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 [83].

A large retrospective cohort study in patients with locally-advanced urethral carcinoma treated with adjuvant RT and surgery vs. surgery alone demonstrated that the addition of RT improved OS [88].

7.3.4 Salvage treatment in recurrent primary urethral carcinoma after surgery for primary treatment

A multicentre study reported that patients who were treated with surgery as primary therapy and underwent surgery or RT-based salvage treatment for recurrent solitary or concomitant urethral disease, demonstrated similar survival rates compared to patients who never developed recurrence after primary treatment [66].

7.3.5 Treatment of regional lymph nodes

Nodal control in urethral carcinoma can be achieved either by regional lymph node (LN) dissection [36], RT [74] or chemotherapy [51]. Currently, there is still no clear evidence supporting prophylactic bilateral inguinal and/or pelvic LND in all patients with urethral carcinoma [53]. However, in patients with clinically enlarged inguinal/pelvic LNs or invasive tumours, regional LND should be considered as initial treatment since cure might still be achievable with limited disease [36]. It was recently shown that in patients with invasive urethral SCC and cN1–2 disease, inguinal LND conferred an OS benefit [53].

7.3.6 Summary of evidence and guidelines for multimodal treatment in advanced urethral carcinoma in both males and females

Summary of evidence	LE
In locally-advanced urethral carcinoma, cisplatin-based chemotherapy with curative intent prior to surgery might improve survival compared to chemotherapy alone, or surgery followed by chemotherapy.	3
In locally-advanced SCC of the urethra, treatment with chemoradiotherapy might be an alternative to surgery.	3
In locally-advanced urothelial- and SCC of the urethra, treatment in academic centres improves OS.	3

Recommendations	Strength rating
Refer patients with advanced urethral carcinoma to academic centres.	Strong
Discuss treatment of patients with locally-advanced urethral carcinoma within a multidisciplinary team of urologists, radiation-oncologists, and oncologists.	Strong
In locally-advanced urethral carcinoma, use cisplatin-based chemotherapeutic regimens with curative intent prior to surgery.	Weak
In locally-advanced squamous cell carcinoma (SCC) of the urethra, offer the combination of curative radiotherapy (RT) with radiosensitising chemotherapy for definitive treatment and genital preservation.	Weak
Offer salvage surgery or RT to patients with urethral recurrence after primary treatment.	Weak
Offer inguinal lymph node (LN) dissection to patients with limited LN-positive urethral SCC.	Weak

7.4 Treatment of urothelial carcinoma of the prostate

Local conservative treatment with extensive TUR and subsequent BCG instillation is effective in patients with Ta or Tis prostatic urethral carcinoma [89]. A systematic review reported patients treated with TURP before BCG show a better local response in the prostatic urethra with a higher disease-free survival (80–100% vs. 63–89%) and progression free survival (PFS) (90–100% vs. 75–94%) than patients in studies in which no TURP was performed [91]. Risk of understaging local extension of prostatic urethral cancer at TUR is high in patients with ductal or stromal involvement [90]. 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 [91, 92]. In 24 patients with prostatic stromal invasion treated with radical cystoprostatectomy, a LN mapping study found that twelve patients had positive LNs, with an increased proportion located above the iliac bifurcation [93].

7.4.1 Summary of evidence and guidelines for the treatment of urothelial carcinoma of the prostate

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

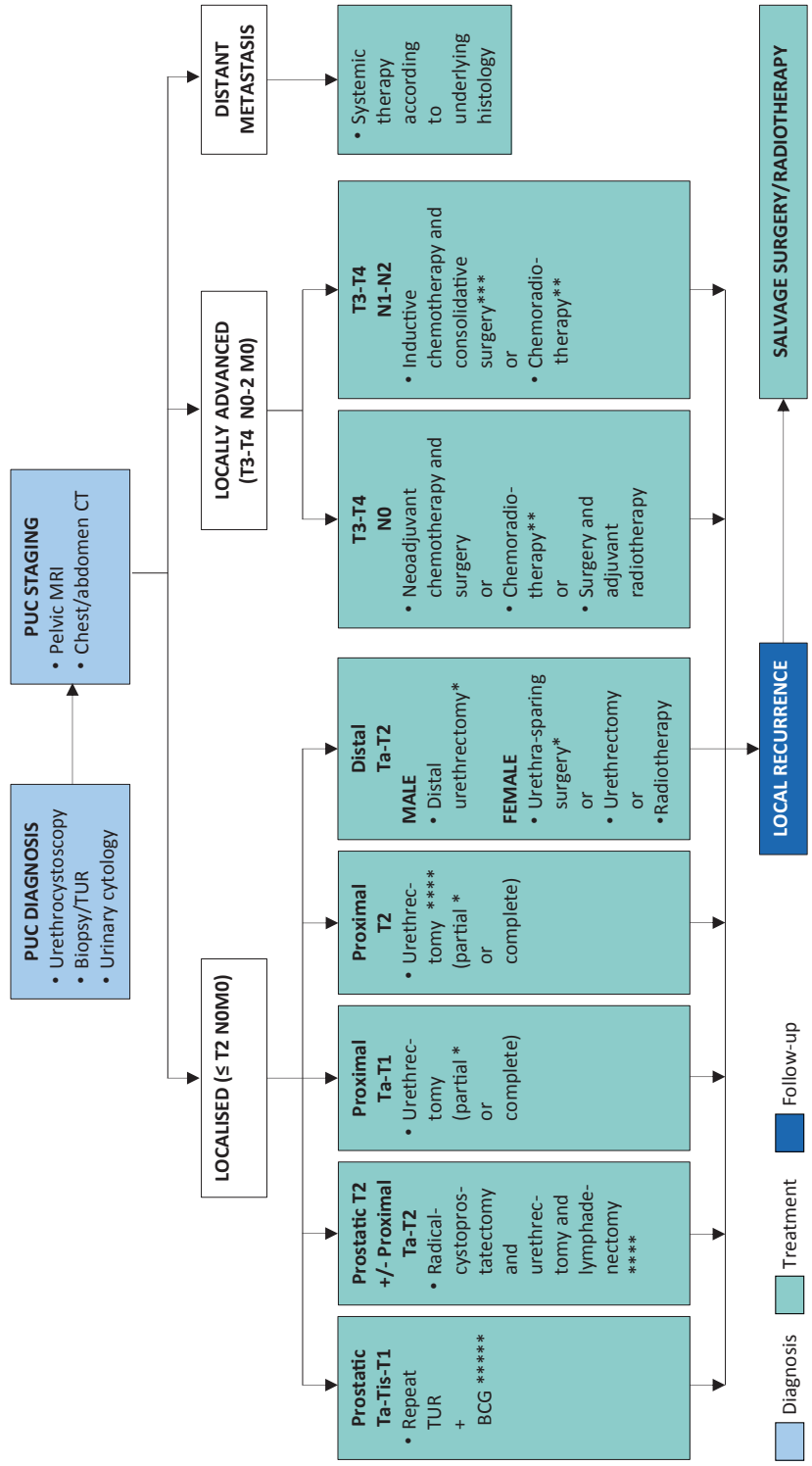
Recommendations	Strength rating
Offer a urethra-sparing approach with transurethral resection (TUR) and bacillus-Calmette Guérin (BCG) to patients with non-invasive urethral carcinoma or carcinoma *in situ* of the prostatic urethra and prostatic ducts.	Strong
In patients not responding to BCG, or in patients with extensive ductal or stromal involvement, perform a cystoprostatectomy with extended pelvic lymphadenectomy.	Weak

7.5 Metastatic disease

A recent analysis of the SEER database reported that patients with M1 disease who underwent primary site surgery did not exhibit any survival benefit [59]. Systemic therapy in metastatic disease should be selected based on the histology of the tumour. The EAU Guidelines on Muscle-invasive and Metastatic Bladder Cancer can be followed if UC is the predominant histology [2]. Even though urethral carcinoma patients have been included in large clinical trials on immunotherapy, so far, in terms of response rates, no subgroup analyses are available [94].

In addition, there is an urgent clinical need to better address the role of local palliative treatment strategies in primary urethral carcinoma including surgery, which has shown to impact positively on QoL aspects in selected patients with advanced genital cancers [95].

Figure 7.1: Management of primary urethral carcinoma



* *Ensure complete circumferential assessment if penile-preserving/urethra-sparing surgery or partial urethrectomy is intended.*

** *Squamous cell carcinoma.*

*** *Regional lymphadenectomy should be considered in clinically enlarged lymph nodes.*

**** *Consider neoadjuvant chemotherapy.*

***** *In extensive or BCG-unresponsive disease: consider (primary) cystoprostatectomy +/- urethrectomy + lymphadenectomy.*

BCG = bacillus Calmette-Guérin; CT = computed tomography; MRI = magnetic resonance imaging; PUC = primary urethral carcinoma; TUR = transurethral resection.

8. FOLLOW-UP

Given the low incidence of primary urethral carcinoma, follow-up has not been systematically investigated. Therefore, it seems reasonable to tailor surveillance regimens to patients' individual risk factors (see Section 6.2). In patients undergoing urethra-sparing surgery, it seems prudent to advocate a more extensive follow-up with urinary cytology, urethrocystoscopy and cross-sectional imaging despite the lack of specific data.

8.1 Research priorities

There are clear gaps in the clinical literature related to the diagnosis, management and follow-up of patients with primary urethral carcinoma. As this is a rare disease, data will likely become available through quality registries and datasets, similar to those currently being set up by the eUrogen initiative.

The Panel identified the following topics as of interest:

- The (long-term) efficacy of urethral-sparing surgery and chemoradiotherapy for genital preservation in localised and locally-advanced tumours;
- The prognostic impact of neoadjuvant and adjuvant treatment modalities in locally-advanced disease;
- The therapeutic benefit and clinical safety of programmed cell death (ligand)-1 inhibitors for the treatment of advanced primary urethral carcinoma;
- The role of MRI in the local assessment of response to therapy.

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10. CONFLICT OF INTEREST

All members of the Muscle-invasive and Metastatic Bladder Cancer Guidelines Panel have provided disclosure statements of all relationships that they have that might be perceived as a potential source of a conflict of interest. This information is open access available on the European Association of Urology website: http://www.uroweb.org/guidelines/primary-urethral-carcinoma/.

This guidelines document was developed with the financial support of the European Association of Urology. No external sources of funding and support have been involved. The EAU is a non-profit organisation and funding is limited to administrative assistance and travel and meeting expenses. No honoraria or other reimbursements have been provided.

11. CITATION INFORMATION

The format in which to cite the EAU Guidelines will vary depending on the style guide of the journal in which the citation appears. Accordingly, the number of authors or whether, for instance, to include the publisher, location, or an ISBN number may vary.

The compilation of the complete Guidelines should be referenced as:
EAU Guidelines. Edn. presented at the EAU Annual Congress Paris 2024. ISBN 978-94-92671-23-3.

If a publisher and/or location is required, include:
EAU Guidelines Office, Arnhem, The Netherlands. http://uroweb.org/guidelines/compilations-of-all-guidelines/

References to individual guidelines should be structured in the following way:
Contributors' names. Title of resource. Publication type. ISBN. Publisher and publisher location, year.

EAU-ASCO Collaborative Guidelines on

Penile Cancer

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1. INTRODUCTION

1.1 Aim and objectives

The European Association of Urology (EAU) - American Society of Clinical Oncology (ASCO) Guidelines on Penile Cancer provide 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 level of evidence available to the experts but following guideline recommendations will not necessarily result in the best treatment-related outcomes for a given patient. Guidelines can never replace clinical expertise when making treatment decisions for individual patients, but rather help to focus decisions. Taking patient's personal values and preferences/ individual circumstances into account is of paramount importance. Guidelines are not mandates and do not purport to be a legal standard of care.

1.2 Panel composition

The EAU-ASCO Penile Cancer Guidelines Panel consists of an international multi-disciplinary group of clinicians, including urologists, pathologists, oncologists, radiation oncologists, and patient advocates. The members of this Panel have been selected based on their expertise and to represent the multi-disciplinary professionals caring for 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. This is an abridged version which may require consultation together with the full text version. This 2023 updated document presents a complete revision of the prior (2018) publication. All prior versions can be viewed at the EAU website: https://uroweb.org/guidelines/archive/penile-cancer.

1.4 Publication history

The EAU Penile Cancer Guidelines were first published in 2000; the current 2023 EAU-ASCO publication presents a complete revision of the prior print. The next update of the Penile Cancer Guidelines will be published in 2026.

1.5 Preface

Penile cancer has a significant impact on quality of life (QoL) in many ways. Patients not only suffer the psychological and emotional stress of a cancer diagnosis and what that means for the rest of their lives, but also the psychological impact and stigma of cancer on an intimate part of the body. The treatments also cause significant physical and emotional changes, resulting in feelings of mutilation, loss of masculinity and coping with the impact on voiding and sexual function, which in turn can result in relationship breakdowns and withdrawal from society. Long-term managing lymphoedema also presents a challenge for many of these men.

As a Guideline Panel, we have chosen to stress the importance of QoL in penile cancer at the beginning of our guidelines, we feel strongly that these significant emotional, social, and physical needs are discussed and addressed early in the patient pathway, through a holistic and multi-disciplinary approach. An important part of a holistic approach is access to palliative care. The World Health Organization (WHO) definition of palliative care states it "*is a crucial part of integrated, people-centered health services. Relieving serious health-related suffering, be it physical, psychological, social, or spiritual, is a global ethical responsibility*" [1]. As a result, access to palliative care should be available to patients throughout their cancer pathway.

It is important to recognise the evolving needs of a patient with a diagnosis of penile cancer, even several months following the completion of treatment, and therefore appropriate follow-up and patient support services are also a critical aspect of penile cancer care.

Reality is that much of the literature on this rare cancer over the last two decades has focused on oncological outcomes rather than functional- and QoL outcomes. So much more needs to be done to investigate these issues and address the many unmet needs of patients diagnosed with penile cancer, some of which are described in Table 1.1 [2].

Table 1.1: Unmet needs of penile cancer patients

Emotional needs	Relationship needs	Medical needs
Loss of masculinity	Impact on relationship with partner	Lack of advice on how to cope
Shock/disbelief	Sexual	Lymphoedema
Depression/sadness	Performance anxiety/cannot satisfy partner	Lack of information on what to expect after surgery
Fear	Concerns on how to tell family	Sit down to urinate/cleanliness of toilets
Anxiety	Relationships damaged or lost	Lack of rehabilitation/supportive care
Embarrassment/stigma	Avoiding meeting friends/new relationships	Missed/incorrect diagnosis

2. METHODS

2.1 Data identification

For the 2023 Penile Cancer Guidelines, new and relevant evidence has been identified, collated and appraised through a structured assessment of the literature. Comprehensive literature searches were done for two major sections: epidemiology, aetiology, pathology and patient support services. Databases searched included Medline, EMBASE and the Cochrane Libraries.

All search histories are available online, as are the protocols and publications of the various systematic reviews (SRs).

For the remaining sections of the text three SRs were conducted:

Review 1. What Is the Most Effective Management of the Primary Tumor in Men with Invasive Penile Cancer: A Systematic Review of the Available Treatment Options and Their Outcomes [3].

Review 2. Management of lymph node-positive penile cancer: a systematic review (in peer review).

Review 3. Systematic review and meta-analysis of minimally-invasive procedures for inguinal nodal staging in penile carcinoma: DSNB and VEIL (manuscript in preparation).

Recommendation within the Guidelines are developed by the panels to prioritise clinically important care decisions. The strength of each recommendation is determined by the balance between desirable and undesirable consequences of alternative management strategies, the quality of the evidence (including certainty of estimates), and the nature and variability of patient values and preferences [4, 5]. This decision process, which can be reviewed in the strength rating forms which accompany each guideline statement, addresses a number of key elements:

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

Strong recommendations typically indicate a high degree of evidence quality and/or a favourable balance of benefit to harm and patient preference. Weak recommendations typically indicate availability of lower quality evidence, and/or equivocal balance between benefit and harm, and uncertainty or variability of patient preference [7].

Additional information can be found in the general Methodology section of this print, and online at the EAU website; http://www.uroweb.org/guideline/. A list of associations endorsing the EAU Guidelines can also be viewed online at the above address.

2.2 Review and future goals

This document was subject to independent peer review prior to publication. Publications ensuing from published SRs have all been peer reviewed.

The results of ongoing SRs will be included in the 2026 update of the ASCO-EAU Penile Cancer Guidelines. One such review is currently ongoing:

- Systematic review and meta-analysis of minimally-invasive procedures for inguinal nodal staging in penile carcinoma: DSNB and VEIL.

3. EPIDEMIOLOGY, AETIOLOGY AND PATHOLOGY

3.1 Definition of penile cancer

More than 95% of penile cancers are SCCs. There are several recognised subtypes of penile SCC with different clinical features and natural history (see Table 3.1). Penile SCC usually arises from the epithelium of the inner prepuce or the glans.

Table 3.1: Histological subtypes of penile carcinomas according to the 2020 WHO Classification [8, 9]**, frequency and outcomes** (Modified from [10])

Subtype	Frequency (% of cases)	Mortality (%)	Other features
HPV-independent SCC			
Usual	45 – 75	20 – 38	Diagnosis of exclusion. Various degrees of differentiation
Pseudohyperplastic*	< 1	0	Well-differentiated, superficially spreading simulating pseudoepitheliomatous hyperplasia
Pseudoglandular*	< 1	30	Poorly-differentiated carcinoma with acantholytic pseudolumina simulating glands
Verrucous	3 – 8	0	Extremely well-differentiated, broad-based, and pushing tumour front. No metastasis reported
Cuniculatum	< 1	0	Endophytic labyrinthine growth pattern with broad-based pushing margins.
Papillary	2 – 15	0 – 6	Papillae covered by well- to moderately differentiated cells without koilocytes
Sarcomatoid	1 -7	45 – 90	Biphasic epithelial and spindle cell neoplasia. Most aggressive and worse prognosis.
Mixed	10 – 19	3 – 7	Two or more subtypes in the same specimen. Prognosis is related to the subtypes involved.
HPV-associated			
Basaloid	4 – 10	21 – 67	Uniform basaloid cells in nests or sheets, with comedonecrosis or abrupt keratinisation.
Warty	5 – 10	0 – 10	Condylomatous papillae with central fibrovascular cores and koilocytes.
Clear cell	< 1	20 – 30	Nests or sheets of cells with ample, clear cytoplasm with central of geographical necrosis.
Lymphoepithelioma-like	< 1	Unknown	Poorly differentiated cells intermixed with dense lymphoplasmacytic and eosinophilic infiltrate.
Mixed	4 - 10	30 - 50	Mainly Warty-basaloid carcinoma according to the WHO 2022.

Others			
SCC NOS (not-otherwise specified)	Unknown	Unknown	Keratinizing carcinoma. This must be used only when evaluation of p16 is not available.
Adenosquamous	1 – 2	0–14	Squamous tumour nests intermixed with a minor mucinous glandular component.
Mucoepidermoid	Unknown	Unknown	Clear separation between adenosquamous and mucoepidermoid is not provided in the WHO classification. Salivary glands criteria can be applied but there is no consensus.

HPV = human papillomavirus; SCC = squamous cell carcinoma; WHO = World Health Organization.
** WHO 2022 classification consider these subtypes part of usual SCC.*
*** This is considered a variant of the cuniculatum carcinoma.*

3.2 Epidemiology

Penile cancer incidence varies across the world (Fig. 3.1). In industrialised countries, penile cancer is uncommon, with an overall incidence of around 0.94/100,000 males in Europe and 0.5 in the USA [11, 12]. In contrast, in South America, Southeast Asia and parts of Africa, the incidence is much higher and can account for 1–2% of malignant disease in men [12]. The annual age-adjusted incidence is 0.7–3.0 in India, 8.3 in Brazil (per 100,000, respectively) and is higher in parts of Africa such as Uganda [12, 13].

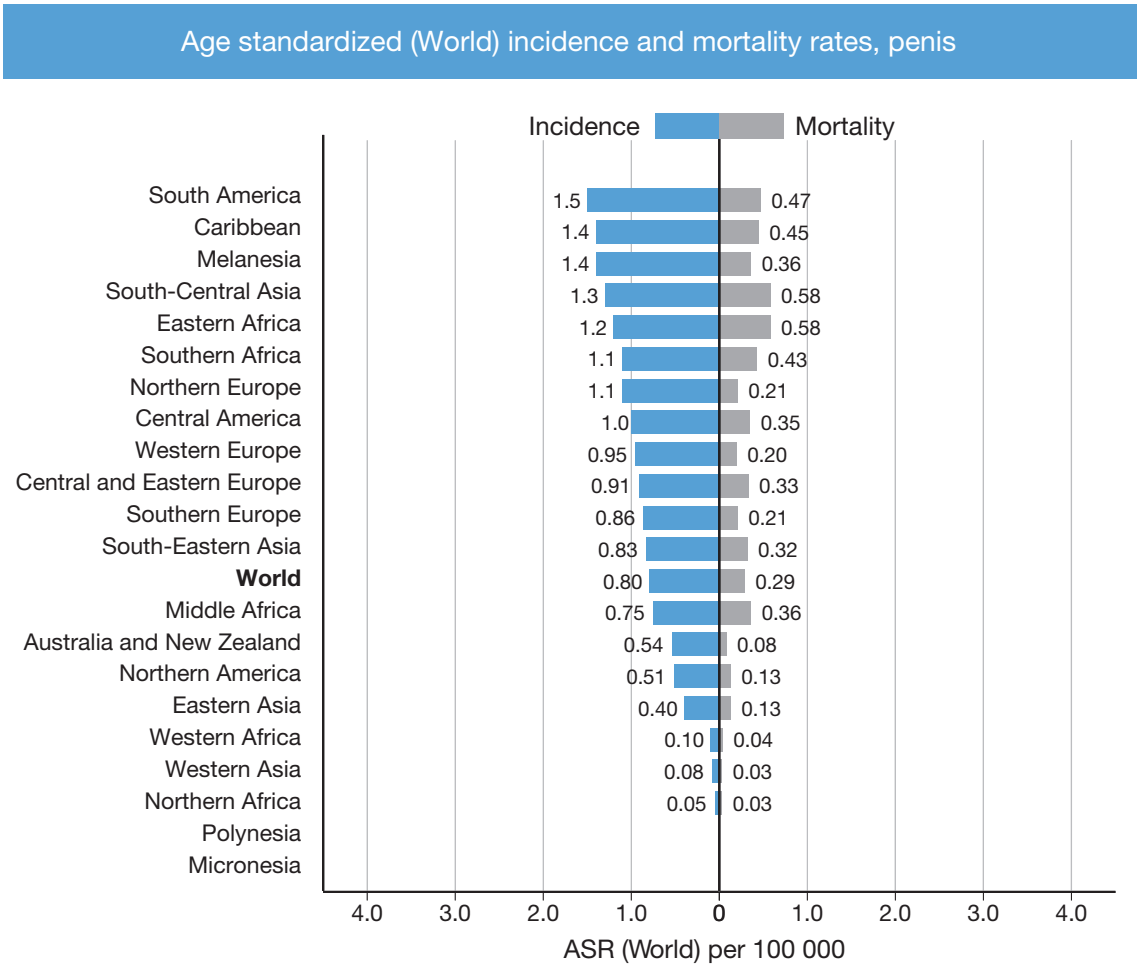
In Europe, there is considerable variation across countries. Data from Norway showed an increase in the age-standardised incidence rates in 5-year periods from 2001-2015 compared to the previous periods (0.65/100,000 in 1956–60 vs. 0.91/100,000, in 2011-2015) with an Estimated Annual Percent Change of +0.80% [14]. In the United Kingdom, the age-standardised incidence rate increased 28% between 1993 and 2018. This trend was seen in age groups from 50–79 years old. Incidence rates remained unchanged for both age extremes (< 50 and > 79 years) [15]. Based on 16 cancer registries in France, incidence rates between 2009 and 2011 were 0.59 per 100,000 men (95% CI: 0.50–0.68) and these rates have remained stable since 1989 [16].

In the USA, the incidence of penile cancer is affected by race and ethnicity, with the highest incidence in white Hispanics (1.01), followed by Alaskans and Native American Indians (0.77), African Americans (0.62) and white non-Hispanics (0.51), per 100,000 males, respectively. The overall age-adjusted incidence rate decreased between 1973 and 2002; per decade from 0.84 (1973–1982), to 0.69 (1983–1992), and 0.58 (1993–2002) per 100,000 males, respectively [17]. An increasing trend, slightly surpassing the previous incidence rates, was described using the Surveillance, Epidemiology and End Result (SEER) 2000–2016 data [18], showing an estimated annual percent change of +3.5% from 2004-2016 [19].

The incidence increases with age [15, 20], with a peak in the sixth decade but it does occur in younger men [21]. Penile cancer is common in regions with a high prevalence of human papillomavirus (HPV), and approximately one-third to half of cancer cases are attributed to HPV-associated carcinogenesis [22, 23]. There are no reports linking this cancer to human immunodeficiency virus (HIV) or acquired immune deficiency syndrome (AIDS).

In summary, it seems that a slight increase in incidence is seen in Western/developed countries, most likely caused by higher infection rates of HPV which is a trend also observed in oropharynx carcinoma [24].

Figure 3.1: Annual incidence rate (world standardised) by world area [25]



3.3 Risk factors, prognosis, and prevention

Several risk factors for penile cancer have been identified, such as phimosis, chronic penile inflammation, lichen sclerosus, smoking, ultraviolet A phototherapy, and low socio-economic status, amongst others [26].

Patient outcome is influenced by clinical and histologic features. United States SEER data from 18 cancer registries indicated an overall 5-year relative survival of 67% with no significant changes when comparing 5-year spans between 2000–2014. Patients with localised disease showed the best outcome with up to 81% 5-year relative survival. Patients with distant metastases have the worst outcomes with only 16% 5-year relative survival [27].

Human papilloma virus infection is the main risk factor for penile cancer [28]. Human papilloma virus deoxyribonucleic acid (DNA) has been identified in intraepithelial neoplasia and invasive penile cancer tissue samples. The HPV virus interacts with oncogenes and tumour suppressor genes (*p16, P53, Rb* genes) [29, 30]. The rate of HPV-positivity differs between different histological subtypes of penile SCC. Human papilloma virus is a co-factor in the carcinogenesis of some subtypes of penile SCC, while others are not related to HPV. The risk of penile cancer is increased in patients with condyloma acuminata [31]. A SR of 52 studies concluded that the overall HPV prevalence in penile cancer is 50.8% (95% CI: 44.8–56.7). Among HPV-associated carcinomas, basaloid carcinoma showed the highest prevalence (84%) followed by warty-basaloid carcinoma (75.7%) and warty carcinomas (58.7%). In histologically HPV-independent carcinomas, HPV prevalence was 19.4%. The most frequent HPV genotypes were HPV16 (68.3%, 95% CI: 58.9–77.1), followed by the low-risk HPV6 genotype (8.1%, 95% CI: 4.0–13.7) [23].

In early studies, HPV has shown an inconsistent association with prognosis. In one study, a significantly better 5-year disease-specific survival (DSS) was reported for HPV-positive vs. HPV-negative cases (93% vs. 78%) [32], while no difference in lymph node (LN) metastases and 10-year survival was reported in another study [33]. This variable relationship with outcome remains unexplained but some studies suggested that it can be related to specific treatment [34] and linked to different histologic subtypes [35]. A meta-analysis published in 2018 [36] reported a pooled HR of 0.61 for penile cancer HPV-positive cases, which is in line with head, neck [37]

and anal cancers [38], with a HR of 0.34 and 0.54, respectively. Positivity for p16 immunohistochemistry (IHC), a surrogate for HPV activity, showed a prognostic value for DSS (hazard ratio [HR]: 0.45) based on two meta-analyses [36, 39]. Similar trends were reported in vulvar and anal cancers [38, 40].

There is no significant association between the incidence of penile and cervical cancer, although half of penile cancer and virtually all cervical cancer cases are linked to HPV [41]. Female sexual partners of patients with penile cancer have not been found to have an increased incidence of cervical cancer [42].

At present, except in a limited number of countries, there is no general recommendation for HPV vaccination in males because of the different HPV-associated risk patterns in penile- and cervical cancer. A meta-analysis showed that the incidence of anal (risk ratio [RR]: 0.42), oral (RR: 0.16), and cervical HPV infections (RR: 0.22) were reduced in vaccinated groups when compared against control groups, indicating that HPV vaccination leads to the prevention of HPV infection [43]. Human papilloma virus vaccination in males showed more than 50% efficacy against anal intraepithelial lesions but no meaningful estimates were obtained for penile, anal, and head and neck invasive carcinomas [44]. Since up to 50% of invasive penile carcinomas and 80% of pre-neoplastic lesions are HPV-associated, HPV vaccination is encouraged [45].

Phimosis is strongly associated with invasive penile cancer [46-49], due to associated chronic infections. However, smegma is not a carcinogen [48]. The incidence of lichen sclerosus is relatively high in penile cancer patients but is not associated with adverse histopathological features, including penile intraepithelial neoplasia (PeIN). Other epidemiological risk factors are cigarette smoking, low socio-economic status, and a low level of education [47, 49].

Neonatal circumcision reduces the incidence of penile cancer; however, it does not seem to reduce the risk of PeIN [46]. The lowest incidence of penile cancer is reported in Israeli Jews (0.3/100,000/year). One matched-pair case-control study reported that the protective effect of neonatal circumcision against invasive penile cancer (OR: 0.41) was much weaker when the analysis was restricted to men without a history of phimosis (OR: 0.79, 95% CI: 0.29–2) [46].

3.4 Pathology

Squamous cell carcinoma accounts for over 95% of penile malignancies. It is not known how often SCC is preceded by premalignant lesions [50-53]. Penile intraepithelial neoplasia is considered the precursor lesion of penile SCC, PeINs are classified into HPV-independent, known as differentiated PeIN, HPV-associated, following the same scheme as the invasive counterparts (see Table 3.2). Clinical terms such as 'Erythroplasia of Queyrat, Bowenoid papulosis and Bowen's disease' are discouraged, based on the 2022 WHO classification [8, 54].

Different histological types of penile SCC with different growth patterns, clinical aggressiveness and HPV associations have been identified (see Table 3.1). Numerous mixed forms exist such as the warty-basaloid form, with 50–60% the most common mixed form, the usual-verrucous (hybrid), usual-warty, usual-basaloid and the usual-papillary, as well as other rarer combinations.

Other malignant lesions of the penis, all much less common than penile SCC, are melanocytic lesions, mesenchymal tumours, lymphomas, and metastases. Penile metastases are frequently of prostatic, urinary bladder or colorectal origin [55]. Different types of penile sarcoma have been reported [8].

Table 3.2: Classification of penile intra-epithelial neoplasia [8]

• **HPV-independent**
o Differentiated PeIN
• **HPV-associated PeIN**
o Common patterns: basaloid (undifferentiated), warty (condylomatous), and mixed
o Other (less frequent) patterns: pagetoid, clear cell, and spindle cell histology

3.4.1 Gross handling of pathology specimens

Tissue sections determine the accuracy of histological diagnosis. Small lesions should be fully included, bigger lesions should have at least 3-4 blocks of tumour with the anatomical landmarks. Specimens should be properly oriented by the surgeons and, in case of circumcision or glans resurfacing, properly pinned to allow clear evaluation of the resection margins. Penectomy specimens must be canalised through the urethra and cut longitudinally in two halves for the evaluation of invasion of the penile structures. In larger tumours identification of distal urethra on gross (as also microscopy) may be difficult. Whole-mount inclusion and sections are recommended as they provide a better background for the appropriate identification of anatomical structures that can improve accurate staging, with a minimal increase in cost [56]. Sentinel LN should be evaluated according to a standardised IHC protocol [57] for detection of micro-metastases; lymphadenectomy/

lymph node dissection (LND) specimens should be inked, and the LNs evaluated properly since extra-capsular extension profoundly influences nodal staging and treatment decisions. Second-opinion pathology review is highly desirable for this rare tumour entity [58], as is setting up comprehensive referral centres for penile cancer management on a national level [58, 59].

*3.4.2 **Pathology report***

For standardisation and data collection purposes the dataset template from the International Collaboration on Cancer Reporting (ICCR) should be used when possible. The pathology report must include the anatomical site of the primary tumour, the histological type of SCC, grade, perineural invasion, depth of invasion, vascular invasion (venous/lymphatic), pattern of invasion, urethral invasion, invasion of corpus spongiosum/corpora cavernosum, surgical margins and p16 IHC results [60-63] (Table 3.3). The confirmation of the presence of HPV in the specimen (e.g., polymerase chain reaction [PCR], *in-situ* hybridization [ISH] for viral DNA/ribonucleic acid [RNA]) is desirable but currently only carried out in research settings.

Table 3.3: Information to include in pathology reports for penile carcinomas

Type of information*	Recommended	required
Clinical information • Prior treatments (topic, radiotherapy, chemotherapy)	x	
Surgical procedure		x
Tumour localisation • Anatomic structures involved externally (e.g.: foreskin, glans, etc.) and in depth (e.g.: dartos, corpus spongiosum, etc.)		x
Macroscopic tumour dimension • Size of tumour • Maximum thickness		x
Photographic documentation	x	
Block identification with description of the localization of the samples		x
Histological tumour type		x
Histological grade		x
Microscopic maximum dimensions • Depth of invasion (i.e., millimetres from basement membrane to deepest point of invasion) • Combination of gross and microscopic if large tumours		x
Extent of invasion (microscopic confirmation of all the involved anatomic structures)		x
Tumour invasion front (Broadly-based pushing, destructive but well-delineated, destructive irregular/finger-like invasion/tumour budding) [64-66]	x	
Lymphovascular invasion [67, 68]		x
Perineural invasion		x
Margin status in mm (margins as per specimen)		x
Lymph node status • Size of largest nodal tumour deposit (not LN size) Total number of LNs, number of positive LNs, extra-capsular spread (ECS), inguinal or pelvic, to be reported in every site separately		x
pTNM Stage		x
HPV assessment (at least p16 IHC based)		x

** See also ICCR dataset: https://www.iccr-cancer.org/datasets/published-datasets/urinary-male-genital/penis/.*

*3.4.3 **Grading***

The tumour, node, metastasis (TNM) classification for penile cancer includes tumour grade based on its prognostic relevance. Tumour grading in penile cancer has been shown to be highly observer-dependent and can be problematic, especially in large tumours which may be heterogeneous. This may have implications on the clinical management, as there may be discordance between biopsy and resection grading [50]. Inter-observer agreement varies according to the experience and specialisation of the pathologist. In general, inter-observer

agreement is poor to moderate (Fleiss' kappa 0.07–0.55) [69]. Nevertheless, until a new methodology to grade penile SCC is developed, grading based on the WHO/The International Society of Urological Pathology (ISUP) classification is recommended (see Table 3.4) with grade 3 and sarcomatoid being considered as poorly differentiated.

Table 3.4: Grading recommendations for penile SCC

Feature	Grade 1	Grade 2	Grade 3	Sarcomatoid
Cytological atypia	Mild	Moderate	Anaplasia	Sarcomatoid
Keratinisation	Usually abundant	Less prominent	May be present	Absent
Intercellular bridges	Prominent	Occasional	Few	Absent
Mitotic activity	Rare	Increased	Abundant	Abundant
Tumour margin	Pushing/well	Infiltrative/ill defined	Infiltrative/ill defined	Infiltrative/ill defined

3.4.4 Pathological prognostic factors

Pathological subtype, peri-neural invasion, lymphovascular invasion [67], depth of invasion and grade in the primary tumour are strong predictors of poor prognosis and high cancer-specific mortality [70]. Higher grade and lymphovascular invasion are predictors of metastatic spread. Lymphovascular space involvement/invasion is often seen in advanced stages but may also be seen in early invasive tumours of high grade and some histologic subtypes [71, 72]. The extent of LN metastasis and extracapsular spread are also strong predictors of prognosis.

Urethral invasion is not considered a prognostic factor (UICC, 8th Edn) [73]. Nevertheless, invasion of the more proximal urethra can signify a highly aggressive SCC with a poor prognosis probably due the invasion of subjacent erectile corpora (see Table 4.1). A SR found that invasion of the corpus spongiosum (pT2) showed better cancer-specific survival (CSS), but no overall survival (OS) benefit compared to invasion of the corpora cavernosa [74]. A modified pT2/T3 has been proposed, taking into consideration high-grade, lymphovascular- and perineural invasion features in response to this inconsistency [75]. Extra-capsular extension in even one single LN carries a poor prognosis and is denoted as pN3 [76-78].

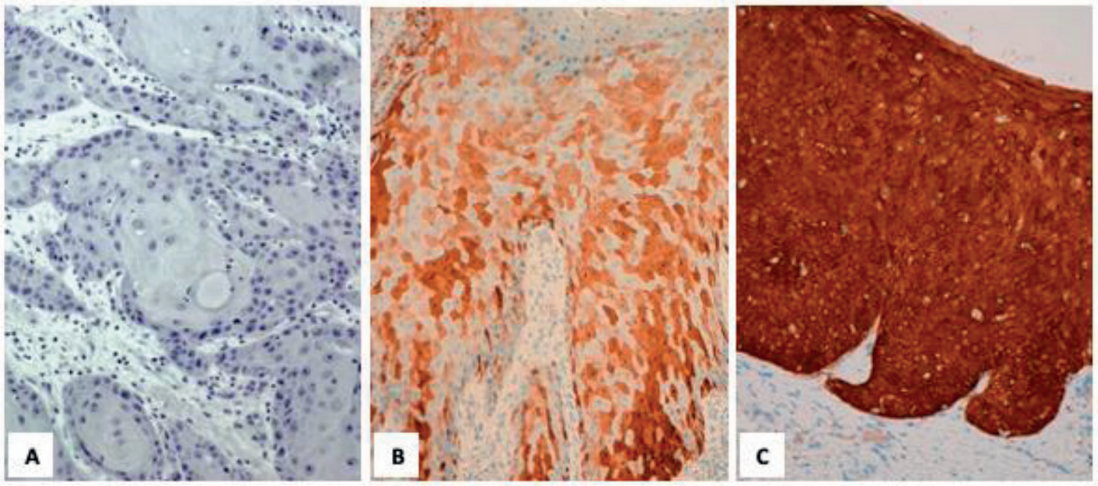
Chaux *et al.*, suggested a prognostic index which incorporates grade, anatomical level of infiltration and perineural invasion to predict the likelihood of inguinal LN metastases and 5-year survival [79]. Sali *et al*., proposed a histopathological risk scoring incorporating grade, anatomical level of involvement and replaced perineural invasion with pattern of infiltration [66]. Other clinical-, pathological- and radiological scores, as well as nomograms have been described but none of these have been comparatively validated which precludes making a recommendation.

3.4.5 Penile cancer and HPV

In the 2022 WHO classification the presence of HPV is a key determinant for the broad classification of penile SCC [8]. However, in most clinical settings, standard molecular assessment of HPV status is not available.

p16 IHC is used as a surrogate for high-risk HPV genotype presence and marker of oncogenic activity. In the absence of more advanced techniques, it is helpful in assigning penile SCC to HPV-associated subtypes. The p16 IHC overall positivity in penile cancer was 41.6% [23]. Higher positivity was seen in morphological HPV-associated SCCs (85.8%) as compared with HPV-independent SCCs (17.1%)[23]. Comparing with RNA ISH, p16 IHC showed a sensitivity of 100% and a specificity of 71%, the latter improved to 89% when considering a high intensity for p16 IHC positivity [80]. These data indicate that sensitivity, specificity, and predictive values for HPV positivity can be improved using the stringent p16 IHC cut-off suggested by Cubilla *et al.* [81] (Figure 3.2). The ISUP reported that 80% of their respondents during a consultation conference on molecular pathology of urogenital cancers used p16 IHC to separate HPV-associated from HPV-independent PeIN and SCCs and made recommendations on the use of p16 IHC [82].

Fig 3.2: Patterns of p16 expression. (A) no staining; (B) mosaic staining pattern: (C) *en-bloc* staining pattern. Only (C) is considered positive for p16.



3.4.6 Penile biopsy: pathological and technical considerations

The quality of biopsy is important [50]. In most cases, acquiring a punch biopsy (e.g., 2–3 mm) under local anaesthesia is sufficient to confirm the diagnosis. In biopsies with an average size of 1 mm, it was difficult to evaluate the depth of invasion in 91% of cases [50]. Furthermore, vascular and lymphatic tumour emboli were detected in only 9–11% of cases [50]. Therefore, in cases where assessment of depth of invasion is necessary, an incisional biopsy which is deep enough to properly assess the degree of invasion and stage is preferable.

3.4.7 Summary of evidence and guidelines for the pathological assessment of tumour specimens

Summary of evidence	LE
Incidence of penile cancer varies according to geographical location, race and ethnicity.	2a
Western developed countries have seen a slight increase in incidence, which may be caused by higher HPV infection rates.	2a
In analogy to other HPV-associated cancers, HPV status may influence DSS of penile cancer, but more data is needed, underlining the importance of routine assessment of HPV status in all penile cancer patients.	2b

Recommendations	Strength rating
The pathological evaluation of penile carcinoma specimens must include the pTNM (see Chapter 4) stage and an assessment of tumour grade.	Strong
The pathological evaluation of penile carcinoma specimens must include an assessment of p16 by immunohistochemistry.	Strong
The pathological evaluation of penile carcinoma specimens should follow the ICCR dataset synoptic report.	Strong

ICCR = International Collaboration on Cancer Reporting.

4. CLASSIFICATION SYSTEMS

4.1 TNM classification

The 8th edition of the UICC/AJCC TNM is the currently used classification system for penile cancer which was last updated in 2017 [73, 83] Compared to the previous (7th) edition, some changes were introduced. The T1 category is stratified into two different risk groups depending on the absence or presence of lymphovascular invasion, perineural invasion, or poor differentiation (T1a vs. T1b, respectively, see Table 4.1) [84]. Furthermore, invasion into the urethra was previously classified as T3 disease. However, a tumour near the meatus

may directly invade into the distal urethra through the corpus spongiosum, which is not associated with worse outcome. In addition, previous studies have shown that corpus spongiosum invasion is associated with a lower incidence of inguinal LN metastasis and has better survival compared to corpus cavernosum invasion. Therefore, invasion into the corpus spongiosum and corpus cavernosum is classified into T2 and T3, respectively [85, 86]. Patients with T4 tumours have extension into adjacent tissues (e.g., prepubic fat, scrotum, spermatic cord, pubic bone, prostate).

The pN1 category was modified to include up to two unilateral inguinal LN metastases, while the pN2 category was modified to be three or more unilateral, or any bilateral LN metastases. This was based on data showing poor outcomes in cases involving three or more unilateral or bilateral LNs compared with those involving one or two unilateral LNs [86, 87]. pN3 stage is defined as pelvic nodes (uni- or bilateral) or presence of extranodal extension (ENE) (inguinal or pelvic, regardless of the number of LN metastases) [73, 83]. Further retroperitoneal LN spread cranial to the pelvic template is classified as extra-regional and therefore as distant metastases.

Table 4.1: UICC/AJCC 8th edition TNM clinical and pathological classification of penile cancer [73, 83]

Clinical classification	
T - Primary Tumour	
TX	Primary tumour cannot be assessed
T0	No evidence of primary tumour
Tis	Carcinoma *in situ* (Penile Intraepithelial Neoplasia – PeIN)
Ta	Non-invasive verrucous carcinoma*
T1	Tumour invades subepithelial connective tissue
T1a	Tumour invades subepithelial connective tissue without lymphovascular invasion or perineural invasion and is not poorly differentiated
T1b	Tumour invades subepithelial connective tissue with lymphovascular invasion or perineural invasion or is poorly differentiated
T2	Tumour invades corpus spongiosum with or without invasion of the urethra
T3	Tumour invades corpus cavernosum with or without invasion of the urethra
T4	Tumour invades other adjacent structures
N - Regional Lymph Nodes	
cNX	Regional lymph nodes cannot be assessed
cN0	No palpable or visibly enlarged inguinal lymph nodes
cN1	Palpable mobile unilateral inguinal lymph node
cN2	Palpable mobile multiple or bilateral inguinal lymph nodes
cN3	Fixed inguinal nodal mass *or* pelvic lymphadenopathy, unilateral or bilateral
M - Distant Metastasis	
cM0	No distant metastasis
cM1	Distant metastasis
Pathological classification	
The pT categories correspond to the clinical T categories. The pN categories are based upon biopsy or surgical excision	
pN - Regional Lymph Nodes	
pNX	Regional lymph nodes cannot be assessed
pN0	No regional lymph node metastasis
pN1	Metastasis in one or two inguinal lymph nodes
pN2	Metastasis in more than two unilateral inguinal nodes or bilateral inguinal lymph nodes
pN3	Metastasis in pelvic lymph node(s), unilateral *or* bilateral or extranodal extension of regional lymph node metastasis
pM - Distant Metastasis	
pM1	Distant metastasis microscopically confirmed

G - Histopathological Grading	
GX	Grade of differentiation cannot be assessed
G1	Well differentiated
G2	Moderately differentiated
G3	Poorly differentiated
G4	Undifferentiated

**Including verrucous carcinoma.*

4.2 Cancer stage grouping

In the UICC TNM 8th edition, stage II was newly subdivided into Stage IIA and Stage IIB based on T categories. Stage IIA is defined as T1b–2N0M0, while Stage IIB is defined as T3N0M0 [73] (Table 4.2).

Table 4.2 UICC TNM Stage/Prognostic Groups [73]

Stage	T	N	M
0	Tis	N0	M0
	Ta	N0	M0
I	T1a	N0	M0
IIA	T1b	N0	M0
	T2	N0	M0
IIB	T3	N0	M0
IIIA	T1–3	N1	M0
IIIB	T1–3	N2	M0
IV	T4	Any N	M0
	Any T	N3	M0
	Any T	Any N	M1

5. DIAGNOSTIC EVALUATION AND STAGING

5.1 Primary lesion

5.1.1 Physical examination

Primary penile carcinoma are usually clinically evident lesions often presenting as raised or ulcerous lesions which can be locally destructive [88]. It is critically important to note that the appearance of penile tumours can be heterogeneous and can sometimes be hidden under the foreskin in case of phimosis. Physical examination should include inspection and palpation of the entire penis (to identify potential skip lesions). The dimensions, anatomic location, and extent of local invasion should be noted, and assessment of stretched penile length is recommended.

5.1.2 Imaging of the primary tumour

Physical examination is a reliable method for estimating penile tumour size and clinical T stage [89]. For distinguishing T1 from T2 disease, magnetic resonance imaging (MRI) does not outperform physical examination. However, when there is uncertainty if the tumour invades the cavernosal bodies (cT3), and if organ-sparing treatment options (e.g., glansectomy) are considered, MRI can be helpful [90, 91]. A SR showed a sensitivity and specificity of MRI in predicting corporal invasion of 80% (95% CI: 70–87%) and 96% (95% CI: 85–99%), respectively [92, 93]. Magnetic resonance imaging can also provide useful information regarding resectability in case of large (T4) tumours with invasion in adjacent structures. Magnetic resonance imaging with and without artificial erection showed similar accuracy in local staging [93]. If MRI is not available, penile ultrasound (US) can be considered [94].

5.1.3 Penile biopsy: indications

A biopsy of the penile tumour should be obtained when there is doubt about the exact nature of the lesion. However, even in clinically obvious cases, histological information from a biopsy can facilitate treatment decisions (such as

indications for surgical staging). Histological confirmation is also necessary to guide management when treatment is planned with topical agents, radiotherapy or laser surgery [88]. For technical and histopathological considerations for penile biopsy see Section 3.4.6.

5.2 Lymph node staging

Penile cancer metastasizes in a stepwise manner through the lymphatic system, initially to the inguinal nodes, then the pelvic nodes and finally to distant nodes [95]. Fewer than 5% of patients will present with distant metastases and these are generally accompanied by regional LN involvement. As a result, the most important prognostic factor for survival of penile cancer is the presence and extent of nodal metastases, with a 5-year CSS of approximately 95%, 80%, 65% and 35% for N0, N1, N2 or N3 disease, respectively [96, 97].

In patients with clinically node-negative groins (no suspicious palpable nodes, cN0), a non-randomised controlled trial (RCT) observed that early LN surgery led to a 3-year survival rate of 84% compared to 35% in those receiving delayed LN surgery, with an ENE incidence of 20% compared to 95% in the early vs. delayed surgery groups, respectively [98]. Therefore, detecting lymphatic spread as early as possible is a crucial element in penile cancer management. Since penile cancer disseminates to the inguinal LNs first, initial LN staging is focused on identifying (micro)metastatic disease in the inguinal LNs as early as possible, and imaging for distant metastases is only indicated in clinically node-positive patients.

*5.2.1 **Physical examination***

Careful palpation of both groins for enlarged/pathologic inguinal LNs must be part of the initial physical examination of patients suspected of having penile cancer. However, reliable physical exmination can be challenging in case of obesity and in patients with previous inguinal surgery. Also, enlarged LNs secondary to infection of the primary tumour (rather than metastasis) can occur. The use of antibiotics with the aim to resolve enlarged nodes may delay further staging and treatment and is not recommended [99]. Based on physical examination, patients can be divided into those without suspicious nodes at physical examination (clinically node-negative, cN0), and those with suspicious palpable nodes (clinically node-positive, cN+). In case of suspected pathologic LNs at palpation; the number, location, size and whether the node is fixed or mobile, should be noted.

*5.2.2 **Clinically node-negative patients (cN0)***

If no suspicious nodes are present at palpation (cN0), approximately 20-25% of patients may still harbour occult metastases, so additional staging is warranted [100].

5.2.2.1 Non-surgical staging options

Unfortunately, there are no validated nomograms or tumour markers that can reliably predict LN involvement. Conventional imaging modalities such as US, computed tomography (CT) or MRI cannot detect micro-metastases, and ^{18}F-fluoro-2-deoxy-D-glucose positron emission tomography (^{18}FDG-PET) does not detect LN metastases < 10 mm [101-103]. Therefore, these imaging modalities are of limited value and are not recommended for routine use in clinically node-negative patients in which the aim is to identify small, sub-clinical, LN metastasis [104, 105]. However, these imaging modalities can be of value to detect enlarged/abnormal nodes in patients when physical examination is challenging (e.g., due to obesity).

In centres that offer dynamic sentinel node biopsy (DSNB) as a surgical staging option (see Section 5.2.2.3.), inguinal US is obtained prior to DSNB. If sonographically suspicious nodes are detected, fine needle aspiration cytology (FNAC) can easily be performed in the same session to confirm the diagnosis of inguinal LN metastasis [106]. Studies incorporating US + FNAC as an initial investigation in clinically node-negative patients prior to surgical staging, reported a sensitivity and specificity of 39% and 100%, respectively. Hence, a negative US is unreliable to exclude LN metastasis in clinically node-negative patients and US should be combined with surgical staging when indicated. However, if US + FNAC is positive, it can reduce the need for DSNB by 10–13%, allowing for additional staging and therapeutic LN dissection at an earlier stage [107, 108]. Therefore, it is recommended to perform US + FNAC in clinically node-negative patients, before surgical staging with DSNB.

5.2.2.2 Indications for surgical staging

Since delayed treatment of occult LN metastasis results in a lower CSS rate and current non-invasive staging options (nomograms, imaging) are not reliable enough to detect micrometastatic disease, invasive/surgical staging remains indispensable to identify micro-metastasis before nodal metastases become palpable/visible [98]. However, surgical staging is over-treatment in the majority of patients since only 20–25% of all clinically node-negative patients harbour occult metastasis.

To select patients that are especially at risk of nodal metastases, risk categories have been established based on T stage, grade of differentiation, and the presence of lymphovascular/perineural invasion in the primary tumour. Well-differentiated (G1), pTa, pTis and pT1 tumours without lymphovascular/perineural invasion (pT1a) are considered low-risk tumours. In patients with low-risk tumours, the risk of metastases is too low to justify surgical staging. Moderately differentiated (G2) pT1a tumours are considered intermediate-risk and are associated with a 6–8% probability of (micro-)metastatic LN disease, whereas in pT1b G2 tumours, the risk is 22–30%. Therefore, all tumours that are stage T1b, or higher, are considered high-risk tumours [72, 109].

Based on these predictors, surgical staging is recommended in all high-risk tumours (T1 with presence of lympho-vascular invasion, peri-neural invasion or poorly differentiated, and T2–T4 with any grade). In intermediate-risk tumours (pT1a G2), the risk of LN metastasis should be balanced against the morbidity of surgical staging on a case-by-case basis.

5.2.2.3 Surgical staging options

By definition, radical inguinal lymph node dissection (ILND) is the most accurate surgical staging method. However, ILND is also associated with the highest complication rates (see Section 6.2 - LN management). To lower morbidity while maintaining sufficient sensitivity, modified ILND templates were developed (consisting of a shorter skin incision; no dissection lateral to the femoral artery or caudal to the fossa ovalis, and preservation of the saphenous vein) [110]. However, modified ILND is still associated with considerable complication rates of 35–49% and false-negative rates of 15–20% [111, 112]. More recently, video-endoscopic/robot-assisted radical LND was introduced (see Section 6.2 - LN management). Initial reports indicate a reduction mainly in wound-related complications compared to open ILND [113]. However, a significant reduction of lymphatic complications is not to be expected since the main predictor of lymphatic complications was shown to be the number of removed LNs [114-116], and the LN yield of the video-endoscopic approach is comparable to open ILND [117].

To avoid resecting unnecessary LNs and thereby minimising the morbidity of surgical staging, DSNB was developed [118]. A sentinel node (SN) is defined as the first LN on a direct drainage pathway from the primary tumour. Based on this concept, it is assumed that if the SN is negative, this indicates the absence of lymphatic tumour spread in the corresponding inguinal basin. In case histopathology identifies SN (micro)metastasis, ipsilateral completion ILND is indicated (see Section 6.2.2) [119]. Dynamic SN biopsy is typically performed using a combination of a radioactive tracer and patent blue dye in order to achieve optimal visualization of the lymphatic drainage system prior and during surgery. Recent innovations include the incorporation of single-photon emission computed tomography/CT (SPECT/CT) and hybrid radioactive and fluorescent tracers [120]. Throughout the years, the procedure has matured into a reliable staging technique with high diagnostic accuracy and low complication rates, especially when performed in experienced centres (sensitivity 92–96%, false-negative rates 4–8%, complication rate 6–14%) [108, 114, 121]. A recent meta-analysis reported a higher pooled false-negative rate of 12% and showed that the false-negative rate was lower in high-volume centres [122]. This might indicate a potential learning curve and supports the call for centralisation of penile cancer care.

If DSNB is not available, and referral to a centre with experience with DSNB is not feasible, or if the patient does not want to run the risk of a false-negative procedure, ILND (modified/superficial/video-endoscopic) can be considered after informing the patient of the inherent risk of higher morbidity associated with these procedures.

*5.2.3 **Clinically node-positive patients (cN+)***

In patients with palpable nodes, nodal metastases are present in approximately 45–80% of cases [123]. Lymph node metastasis should preferably be histopathologically confirmed by image-guided biopsy (e.g., US or CT). While in cN0 patients further abdominal and thoracic imaging is not recommended (See Section 5.2.2.1), it is of value in cN+ patients to clinically stage the pelvis and exclude distant metastases. Computed tomography of the chest/abdomen is broadly available, however CT has a sensitivity of only 20–38% for the detection of pelvic LNs. Magnetic resonance imaging constitutes another diagnostic staging modality; in particular in those patients with a contra-indication to iodine-based contrast agents who cannot be staged by CT. A meta-analysis comparing CT and MRI showed comparable results with a pooled sensitivity of 42% for CT and 39% for MRI and pooled specificity was 82% for both [124]. Imaging with ^{18}FDG-PET/CT is likely to be more accurate than CT alone in the pre-operative staging of pelvic LNs, as shown in other malignancies [125]. In penile cancer, ^{18}FDG-PET/CT showed a sensitivity and specificity of 91% and specificity of 100%, respectively, for the detection of pelvic metastases in patients with an US + FNAC-confirmed positive inguinal LN [126]. In patients initially staged as cN0 and who are subsequently upstaged to pN+ at surgical staging, additional imaging of the chest/abdomen should also be considered. Treatment of node-positive disease is further discussed in Section 6.2.

5.3 Summary of evidence and guidelines for the diagnosis and staging of penile cancer

Summary of evidence	LE
For distinguishing T1 from T2 disease, MRI does not outperform clinical staging.	2b
For predicting corporal invasion (T3 disease), MRI showed a pooled sensitivity and of 80% (95% CI: 70–87%) and 96% (95% CI: 85–99%), respectively.	2b
Magnetic resonance imaging with and without artificial erection showed similar accuracy in local staging.	2b
Computed Tomography, PET/CT and MRI imaging cannot detect micro-metastases and are therefore of limited value in clinically node-negative patients in which the aim is to identify small sub-clinical LN metastasis.	2a
Inguinal US + FNAC of sonographically abnormal nodes can reduce the need of DSNB when tumour positive, allowing for earlier therapeutic treatment of node-positive disease.	2a
For surgical staging of cN0 patients, DSNB has shown a high diagnostic accuracy.	2a
Sentinel node biopsy has been shown to lower complication rates compared to modified-, superficial-, or video-endoscopic inguinal LND.	2b
Imaging with ^{18}FDG-PET/CT in clinically node-positive patients showed higher sensitivity/specificity than CT alone in the pre-operative staging of the pelvic LNs and distant metastasis.	2b

Recommendations	Strength rating
Primary tumour	
Perform a detailed physical examination of the penis and external genitalia, recording morphology, size and location of the penile lesion, including extent and invasion of penile (adjacent) structures.	Strong
Perform magnetic resonance imaging (MRI) of the penis/primary tumour (artificial erection not mandatory) when there is uncertainty regarding corporal invasion and/or the feasibility of (organ-sparing) surgery. If MRI is not available, offer ultrasound (US) as alternative option.	Weak
Obtain a pre-treatment biopsy of the primary lesion when malignancy is not clinically obvious, or when non-surgical treatment of the primary lesion is planned (e.g., topical agents, laser, radiotherapy).	Strong
Inguinal lymph nodes (LN)	
Perform a physical examination of both groins. Record the number, laterality and characteristics of any palpable/suspicious inguinal nodes.	Strong
Clinically node-negative (cN0)	
If there are no palpable/suspicious nodes (cN0) at physical examination, offer surgical LN staging to all patients at high risk of having micro-metastatic disease (T1b or higher).	Strong
In case of T1a G2 disease, also discuss surveillance as an alternative to surgical staging with patients willing to comply with strict follow-up.	Weak
When surgical staging is indicated, offer dynamic sentinel node biopsy (DSNB). If DSNB is not available and referral is not feasible, or if preferred by the patient after being well informed, offer inguinal lymph node dissection (ILND) (open or video-endoscopic).	Strong
If DSNB is planned, perform inguinal US first, with fine needle aspiration cytology (FNAC) of sonographically abnormal LNs.	Strong
Clinically node-positive (cN+)	
If there is a palpable/suspicious node at physical examination (cN+), obtain (image-guided) biopsy to confirm nodal metastasis before initiating treatment.	Strong
In cN+ patients, stage the pelvis and exclude distant metastases with ^{18}F-fluoro-2-deoxy-D-glucose positron emission tomography (^{18}FDG-PET) computed tomography (CT) or CT of the chest and abdomen before initiating treatment.	Strong

6. DISEASE MANAGEMENT

6.1 Treatment of the primary tumour

Besides its role in sexual functioning and urination, a fully functional penis is central to a patient's sense of wholeness, desirability and masculinity. Hence, the aims of the treatment of the primary tumour are complete tumour removal with as much organ preservation as possible, without compromising oncological control.

There are no RCTs or observational comparative studies for any of the treatment options for localised penile cancer. Penile preservation appears to be superior in functional and cosmetic outcomes as compared to partial or total penectomy and is considered to be the primary treatment method for localised penile cancer, based on retrospective studies.

Histological diagnosis and local staging must be obtained before non-surgical treatments can be considered. For small tumours, excisional biopsy can equal treatment, while for larger lesions which necessitate more complex or mutilating surgery, an incisional biopsy is advised (see Section 3.4.6). Histology provides confirmation of the diagnosis before treatment and informs on the risk group of the primary tumour which has important consequences for invasive staging of the groins. With surgical treatment, negative surgical margins for invasive carcinoma must be obtained. Treatment of the primary tumour and of the regional nodes can either be simultaneous or staged.

Local treatment modalities for small and localised penile cancer include topical therapy, laser ablation, excisional surgery, external beam radiotherapy (EBRT) and brachytherapy. Unfortunately, the SR of the Guidelines Panel revealed a complete absence of both RCTs and prospective trials assessing and comparing the effectiveness of interventions for managing the primary tumour [3]. Treatment recommendations can therefore only be based on retrospective data and expert opinion. In the absence of comparative evidence supporting treatment modalities, patients should be informed about all appropriate treatment options for their specific tumour and situation, and the potential advantages and disadvantages for each technique which are discussed per disease stage in the following sections.

*6.1.1 **Treatment of superficial non-invasive disease (PeIN, Ta)***

Penile intra-epithelial neoplasia can progress to invasive lesions in 2.6–13% of patients, despite treatment; hence, definitive eradication and diligent follow-up monitoring are important [127-129]. Most PeIN lesions are located on the mucosal surfaces of the glans or prepuce whilst lichen sclerosus also affects the prepuce [128]. Thus, circumcision should be the primary surgical option [129]. Following circumcision, the glans mucosa keratinizes over a period of 3–6 months and any residual PeIN or lichen sclerosus may resolve. Close monitoring before starting additional therapy has been advocated, but to date, data supporting this concept are limited [129]. Considering a median time to progression to malignancy of thirteen months [128], this approach seems reasonable to test in future clinical trials.

6.1.1.1 Topical therapies

Topical therapy with imiquimod (IQ) or 5-fluorouracil (5-FU) are effective non-invasive first-line treatment options which use is increasingly reported [130]. 5-Fluorouracil exerts its effects through inhibition of the enzyme thymidylate synthase. Although no standard protocol exists, leaving the 5-FU ointment on for 12 hours every 48 hours during a 4 to 6-week treatment course is often recommended in reported series of PeIN therapy [131]. Imiquimod acts through several pathways including activation of immune cells via toll-like receptor 7, creating an inflammatory response, and is commonly used 3 times per week for 12 weeks. There is no consensus or comparative data on the optimal treatment schedules for these therapies and the evidence for these treatments is heterogenous as it only relies on retrospective studies. A SR based on the aforementioned low-quality data illustrated that topical agents showed response- and recurrence rates of 40–100% and 20% for IQ, vs. 48–74% and 11% for 5-FU, respectively [132]. Because use of 5-FU typically results in marked erythema, erosions, and crust lasting for a month or longer, decreased patient compliance with treatment regimens may result in diminished effectiveness. Similarly, IQ use is complicated by the resultant tissue effects, including erythema, oedema and erosions, ulceration and crust, that are not consistent from one individual to the next [133]. Discontinuation of topical agents because of side effects was observed in 12% of cases [132]. It is advised that treatment effects must be clinically assessed and in cases of doubt evaluated by biopsy and long-term surveillance is warranted. Insufficient responses and recurrences may signify underlying invasive disease, hence, if topical treatment fails, it should not be repeated.

6.1.1.2 Laser ablation

Laser ablation is an alternative treatment option. Energy-based therapies discussed in the literature include Neodymium:Yttrium-Aluminium-Garnet (Nd:YAG, penetration 4–6 mm, wavelength 1064 nm) or Carbon dioxide (CO_2, penetration < 1 mm, wavelength 10600 nm) lasers and photodynamic therapy [134]. Laser treatment

has shown total response rates of 52–100% with recurrence reported in 7–48% of patients [132]. Altered penile sensitivity following laser treatment has been described, including increased sensitivity in 50% and decreased sensitivity in 15% of patients. Reports show relatively high rates of local recurrence, possibly owing to inadequate penetration, difficulties in assessing borders of affected areas and missing lesions that have invaded the subepithelial tissue [10, 135, 136]. Repeat laser treatment for recurrence has been described in some series without compromising long-term oncological outcomes, which is likely a result of the low risk of the lesions treated in those series [137, 138]. For cryotherapy, with or without topical therapy, and photodynamic therapy, which induces photo-selective cell death, there are only limited data for the treatment of PeIN.

6.1.1.3 Surgery

Extensive PeIN, residual PeIN in resection margins or recurrent disease after ablative or topical therapy, can be treated by surgical excision. Glans resurfacing consists of full thickness removal of the glandular epithelium followed by reconstruction with a graft (split skin [139] or buccal mucosa for urethral reconstruction [140]). Grafts tend to have excellent engraftment rates on this well-vascularized wound bed [141]. Recurrences are reported to be low (0–20%) and cosmesis is acceptable [139, 141, 142]. If feasible, preservation of the coronal ridge helps maintain sexual function and provides excellent cosmetic outcomes as shown by a small retrospective report [143]. Resection, as opposed to ablative or topical treatments, provides the advantage of complete histopathological local staging and detection of areas of invasion; in one study in cases of glans resurfacing for presumed PeIN, up to 20% of patients were found to have invasive disease on histopathological examination [139]. Surgeons and pathologists are urged to discuss appropriate specimen handling (e.g., pinning down the skin as resected) and pathological reporting of these cases to aid further management and avoid over-reporting of positive margins [144].

*6.1.2 **Treatment of invasive disease confined to the glans (cT1/T2)***

When feasible, small and localised invasive lesions should receive organ-sparing treatment. Resection of the primary lesion not only eradicates all disease in localised invasive tumours but also provides definitive pathological staging without the risk of understaging and of missing intra-tumour heterogeneity encountered with incisional or punch biopsy [10]. Foreskin tumours are treated by 'radical' circumcision. For glandular and coronal lesions, wide local excision, partial glansectomy or total glansectomy with reconstruction, are surgical options while additional circumcision is advised in glandular tumours. External beam radiotherapy and brachytherapy are radiotherapeutic options for these patients. Laser therapy of small lesions has been reported but the risk of invasive disease must be recognised, and the recurrence risk is high, possibly as a result of the limited tissue penetration depth of laser ablation. Further research is needed to better establish the comparative safety and effectiveness of surgical and nonsurgical therapies for penile cancer.

Treatment choice depends on tumour size, histology, stage and grade, localisation and patient preference. Over the recent decades, a shift towards organ-sparing surgery has been observed, based on the assumption that local recurrence has little influence on long-term survival. However, in a large series looking at higher-risk tumours treated with glansectomy [145] or partial penectomy [146], it was observed that patients experiencing local recurrence have poorer survival, also in multivariate analysis correcting for poor prognosticators. This, however, does not indicate that these patients may have fared better with more radical excision, as local recurrence in those cases may be a display of a more aggressive disease biology in general. On the other hand, large series are available showing lower local recurrence rates after amputative surgery despite more aggressive tumours, supporting a wider resection [147].

The SR by the Panel found a cumulative 5-year recurrence free rate (RFR) of 82% in case series and 76.7% in non-RCTs for organ-sparing surgery. Similarly, the cumulative 5-year RFR of amputative surgery is reported 83.9% in case series and 93.3% in controlled studies. These variations reflect the differences of study designs as well as the different cohorts analysed at each instance; a larger proportion of patients treated with amputative surgery typically present with advanced disease (≥ T3: 29.4% vs. < T3: 7.8%). The higher RFRs observed after amputative surgery needs to be weighed against the impact on sexual function and QoL. Hence, the limits of organ-sparing surgery are not completely clear, and the higher risks of local recurrence should be discussed with the patient when making a treatment plan.

6.1.2.1 Width of negative surgical margins

The concept of organ-preserving surgery is based on observations of how the distance between tumour and resection margin affects local recurrence. A study found that most lesions do not spread > 5 mm beyond the macroscopic margin and, in line with this finding, subsequent reports show that an excision margin of between 5 mm and 10 mm results in acceptably low recurrence rates [148-150]. Another study from a supra-regional referral centre found that local recurrence rates only increased considerably when the distance from tumour to margin was

< 1 mm [151]. However, comparative evidence is lacking for this topic and there is no clear evidence as to what constitutes an oncologically safe width of macroscopic negative surgical margins. Based on the observation that in lower-risk tumours (1) a local recurrence does not impact survival and (2) minimal section margins > 1 mm do not result in a higher risk for local recurrence, macroscopic margins can indeed be minimal, specifically in smaller and less aggressive lesions. Hence, to ensure complete removal with histologically negative margins, standard excision must include a margin of clinically normal-appearing skin around the tumour and surrounding erythema. However, for bulky or higher-grade lesions where local recurrence may have an impact on survival, adoption of a wider margin or partial penectomy may be prudent and should be discussed with the patient [145, 150].

6.1.2.2 The use of intra-operative frozen section assessment

The role of frozen section and its value in the interpretation of excision margins remains uncertain, potential benefits of adopting frozen section assessment include a decreased risk of local recurrence and a smaller safety margin, allowing maximum preservation of penile tissue. A study in 169 patients treated in a tertiary referral centre in the UK showed that frozen section use during organ-sparing surgery contributed to a very low definitive positive margin rate of 0.6% and a local recurrence rate of 5.3% [152, 153]. These data, however, are contradicted by a large contemporary series, also from a tertiary referral centre in the UK, showing similarly low local recurrence rates of 4% without routine intra-operative frozen section analysis [151]. A SR conducted in 2017 stated that routine frozen section analysis results in lower rates of local recurrence but failed to correct for patient selection, and hence a causal relationship between frozen section analysis and low local recurrence rates is lacking, as is comparative research. Data from one multi-centre study suggests that differentiated PeIN, squamous hyperplasia and lichen sclerosis present at the surgical margins are frequent findings and are not relevant for CSS [77]. As negative surgical margins are aimed for, in cases of doubt on the radicality of the resection, it is the Panel's opinion that frozen section analysis is a helpful tool to achieve definitive tumour-free margins, whereas it is not recommended to be used routinely.

6.1.2.3 Laser ablation

In line with results achieved in non-invasive and superficially-invasive penile lesions, laser ablation has been proposed as an option for smaller invasive lesions. Typically, a CO_2 laser can resect the tumour with ample millimetres of margin, while for coagulation of the tumour bed a Nd:YAG laser is the better option as it provides deeper uniform tissue coagulation. Healing time is fastest after CO_2 laser treatment, with re-epithelization almost complete by three to six weeks post-treatment. Because of the greater depth of tissue coagulation, the healing time for Nd:YAG laser treatment is longer, often up to six weeks [134]. Penetration depth depends on laser type and settings and most commonly used settings are 15–20 W for CO_2 and 15–25 W for Nd:YAG lasers but only very few publications provide technical details [134].

In the Panel's SR, seven studies reported outcomes of laser therapy for invasive penile cancer limited to T1 (81.2%) or T2 (18.5%) disease in a total of 389 patients [3]. Five-year RFR ranged from 34.2-94%. The cumulative mean 5-year RFR was 69.4% (270/389). Three studies reported a 5-year RFR per disease stage of 42.9–73.9% for T1 and 23.5%–84.2% for T2 disease. In nine studies (n = 512), the penile preservation rate following laser therapy was 50–100% (mean 89.2%), indicating that a large proportion of recurrences had to be managed with total amputation, which raises caution on the use of such technique and its use is likely best limited to T1 tumours. Tang *et al*., demonstrated that nodal recurrence was high in a multi-institutional cohort of patients treated with laser ablation as monotherapy, illustrating the importance of pre-ablation biopsy for risk stratification and nodal staging. Clinicians should be aware of the risk of understaging as a result of incision biopsy followed by ablation vs. complete resection [10, 154], and it is advised that patients be informed that laser therapy may result in higher local recurrence rates when compared to surgical excision.

Three studies reported on laser-related complications, with preputial oedema and dysuria reported most frequently. Meatal stenosis was reported in 7.4% and post-operative bleeding in 1–7% of patients. Three studies assessed the sexual function after laser treatment and 46.0–56.5% of men report an impact on their sexual life. A single trial including 46 men found that 72% reported no change in erectile function, 22% reported decreased erectile function and 6% reported improvement [155].

6.1.2.4 Moh's micrographic surgery

Moh's micrographic surgery is a surgical technique by which tissue is excised and processed with en face histological margins in real time to give a complete circumferential and deep margin. It aims at maximal organ-preservation by adopting margin-guided excision. Three studies reported the 5-year RFR in 51 men, most with T1 disease. Recurrence-free rates ranged from 71.4 to 100% with a cumulative mean 5-year RFR of 88.2% (45/51) [3]. As data are very limited, it is not routinely recommended, and the Panel feels it is important to involve a clinician experienced in penile cancer management before referral for Moh's surgery.

6.1.2.5 *Wide local excision and circumcision*

In addition to treating preputial penile cancer, circumcision combined with topical treatment, laser therapy or brachytherapy, facilitates follow-up examinations [153]. For small, distal preputial penile cancer, circumcision alone usually presents adequate treatment. However, lesions located on the corona or glans, limited in size, may be treated with wide local excision which should include a margin of clinically normal-appearing skin around the tumour and surrounding erythema (see Section 6.1.2.1). Few data on wide local excision are available, the technique has, so far, only been described in retrospective series combining various types of organ-sparing treatments.

6.1.2.6 *Glans resurfacing*

Besides its established effects in the therapy of PeIN, total or partial glans resurfacing has been reported to be employed for superficially-invasive lesions combined with deeper resection at the site of invasion. The literature is heterogeneous with many studies reporting miscellaneous techniques of organ-sparing surgery including glans resurfacing without specification of tumour invasiveness in these patients specifically. Five studies have reported results of glans resurfacing specifically in invasive penile cancer in a total of 68 patients, with most being pT1 and a few instances of T2 lesions displaying RFR ranging from 75–96.6% [143, 151, 156-158]. Similar to glans resurfacing as applied to carcinoma *in situ*, graft-related complications are scarce and cosmesis, as assessed by patients, is generally good. Cakir and colleagues have described a small series using a technique for glans resurfacing with preservation of the coronal sulcus for distal tumours not invading the sulcus and show that this option can be considered when aiming for maximally preserved erogenous sensation [143].

6.1.2.7 *Glansectomy*

Patients with tumours confined to the glans and prepuce that are not eligible for wide local excision or glans resurfacing are good candidates for glansectomy. Patients with poor vascular function, diabetes, immunosuppression, or previous radiation to the groin area are less suitable for graft application due to higher failure rates which should be discussed with the patient when making the decision between graft application for primary closure. For cases in which the lesion is confined to the glans and is clearly away from the corporal tips according to imaging or clinical examination, an approach that uses dissection over Bucks' fascia can be used to excise the glans, while in cases of doubt, a plane under the Bucks fascia can be used. In the Panel's SR, glansectomy with or without resection of the outermost tips of the corpora cavernosa was assessed in six studies including 1,681 men, 86.4% of whom with T1–T2 disease. The 5-year RFR ranged from 78.0–95.8% [3]. A split-thickness skin graft is commonly used to reconstruct a neo-glans and the graft loss rate was 1.5–23.5%. The incidence of meatal stenosis in a recent SR was 2.8–14.3%. Good cosmetic outcomes and normal erections were reported in 95–100% and 50–100% of cases, respectively [159]. In a large retrospective study by Roussel and colleagues, describing a multicentre cohort including 230 pT1, 534 pT2 and 108 pT3 patients treated in high-volume centres, the authors found high-grade disease and pT3 to be independent risk factors predicting local recurrence. Three-year local RFS rates were 94.8%, 87.3% and 69.7% in patients with no, one, or both, risk factors, respectively. Moreover, in this population, local recurrence remained a significant predictor of decreased overall- and CSS, even when excluding margin-positive cases, patients with pT3 disease, and patients with clinical LN involvement. Hence, these issues should be discussed with the patient prior to surgical intervention when choosing between glansectomy and the more aggressive partial penectomy.

6.1.2.8 *Partial penectomy*

Amputative and partial amputative surgery is reserved for more advanced disease. Results of partial or total penectomy were reported in 5 heterogeneous studies with a total of 243 patients. 71.6% of men were staged as T1–T2 and the 5-year RFR was 75.8-95.4%. The cumulative mean 5-year RFR was 83.9% (204/243). Two cases series including T1 and T2 men, reported 92% and 95.4% 5-year RFRs after partial penectomy [3]. There is no comparative evidence between partial penectomy and glansectomy for T1–T2 lesions, however most case series report similar RFRs between penile-sparing surgery and amputative surgery. In a series of T1 and T2-only disease, 5-year RFR after amputative surgery were superior to penile-sparing surgery, indicating that a wider resection is protective against local recurrence and should always be discussed as an alternative option, although the higher RFRs observed after amputative surgery needs to be weighed against the impact on sexual function and QoL.

6.1.2.9 *Radiotherapy for T1 and T2 disease*

Radiotherapy is an organ-preserving approach with good results in selected patients with T1–2 lesions [3]. It can be given as external radiotherapy with a minimum dose of 60 Gy EQD2 combined with a brachytherapy boost or as brachytherapy alone [160, 161]. Brachytherapy has been studied only for lesions < 4 cm hence its use should be limited to tumours not exceeding this size. Reported results are best with brachytherapy with

local control rates ranging from 70–90% [160, 161]. The American Brachytherapy Society and the Groupe Européen de Curiethérapie-European Society of Therapeutic Radiation Oncology consensus statement for penile brachytherapy also reported good tumour control rates, acceptable morbidity, and functional organ preservation for penile brachytherapy for stages T1 and T2 disease [160]. Penile preservation rates of 70–88% have been reported [162], with overall penile conservation rates of 87% and 70% at 5 and 10 years. Pulsed-dose-rate brachytherapy can be used interchangeably with traditional low-dose rate and 15% local recurrences have been reported in one series [163]. High-dose rate brachytherapy has been introduced but experience is still limited [164-169].

The Panel's SR identified 21 studies evaluating the efficacy of radiotherapy for the management of primary tumour in men with penile cancer. A total of 1,222 men had low-, pulse-, or high-dose rate brachytherapy after circumcision [3]. The cumulative mean 5-year RFRs were 78.6% (861/1,096) after brachytherapy and 55.2% (37/67) after EBRT. Four studies (including some EBRT and some brachytherapy cohorts) reported RFRs per disease stage, with 5-year RFRs for T1 ranging from 59–94%, 50–67% in T2, and 17–77% in T3 disease [167, 170-172].

In the few studies comparing surgical treatment and radiotherapy, results of surgery were slightly better. In a meta-analysis comparing surgery and brachytherapy, 5-year OS and local control rates were 76–84% for surgery and 73–79% for brachytherapy, respectively [173]. The organ preservation rate for brachytherapy was 74% and there was no difference in survival. Local recurrence after radiotherapy can be salvaged by surgery [170].

Specific complications of radiotherapy for penile cancer are urethral stenosis (20–35%), glans necrosis (10–20%) and late fibrosis of the corpora cavernosa [174]. With brachytherapy, meatal stenosis has been reported to occur in up to 40% of cases but was much lower in a contemporary series of 73 patients with only 6.6%. In that series, 2.6% of patients reported pain with sexual intercourse and 5.3% dysuria over a follow-up of 5 years. Penile amputation for necrosis was necessary in 6.8% of patients [175].

Functional outcome after radiotherapy has not often been reported. In one report, 17/18 patients with normal erections before treatment maintained these after treatment [176]. After a minimum of 3 years (median 5.9) follow-up after brachytherapy treatment, 29/34 patients (median age 63 years) answered a self-reporting questionnaire. Urethral dilatation had been necessary in 30% of patients, self-catheterisation in 13%; erectile dysfunction was mild and 70% continued to maintain sexual activity, and QoL was good.

*6.1.3 **Locally advanced disease (T3–T4)***

6.1.3.1 Resectable disease

In cT2 disease where there is doubt of corporeal or tunica albuginea invasion, rather than continuing the dissection over Buck's fascia to perform glansectomy combined with distal corporectomy, dissection superficial to the tunica albuginea can be adopted after dividing the neurovascular bundle. In these instances, frozen sections of the corporeal tips and urethra may be helpful in assessing the radicality of the procedure peri-operatively. Pre-operative MRI or US can assist in surgical planning as discussed in Chapter 5. For cT3 patients with obvious involvement of the corpora cavernosa, partial amputation is standard. Patients can be offered reconstructive options such as urethral centralisation and/or neo-glans formation with the use of a graft. Two studies in higher-risk patients treated with radical glansectomy or partial penectomy show that local recurrence in these instances is associated with poor survival. Patients should be informed that a wider resection (i.e., partial or radical penectomy) provides a lower risk of local recurrence at the cost of functionality of the penis [145, 177]. Radical amputation and diversion of urination with a perineal urethrostomy is reserved for those patients in whom a resection with a safe margin would result in the inability to void standing upright or without wetting the scrotum. Radiotherapy for locally-advanced penile lesions should be undertaken with concurrent chemotherapy. As with disease in the LNs, traditional radiotherapy dosing recommendations are being reconsidered [178]. Complex treatment planning will be necessary in most cases of T3–T4 primary lesions, with patient-unique immobilization to spare testes and scrotum. A total phallic reconstruction may be offered to patients undergoing total/subtotal amputation. Extensive partial amputation with wide margins or total penectomy with perineal urethrostomy is the standard advisable treatment. In case of locally-advanced and ulcerated cases which are resectable, composite myocutaneous flaps or advancement flaps may be needed to cover the surgical defect [179].

6.1.3.2 Non-resectable disease

In non-resectable disease, induction chemotherapy offers the ability to downstage disease and thereby enable surgical resection among responders, even among men with advanced penile cancer. Several retrospective- and prospective series have evaluated the effects of combination regimens using paclitaxel or docetaxel with cisplatin and ifosfamide or 5-FU. The combination of irinotecan and cisplatinum, and vinflunine as monotherapy, have also been investigated. Although there is considerable heterogeneity in the regimens and cohorts combining advanced nodal disease and unresectable primary tumours, objective responses are observed in

29–60% of patients [177, 180-186] . In two recent SRs pooled ORR were 53–57% [187] with pooled objective response rates of 57% (95% CI: 46–67%) for taxane-platinum combinations and 54% (95% CI: 31–76%) for non-taxane platinum combinations [188], and pathological complete responses in 4–10% [188], at the cost of considerable toxicity. This approach is discussed in more detail in Section 6.4.1.1. In case of not obtaining a response sufficient for resection, palliative chemo-radiotherapy is an option.

Accumulated evidence in anal and vulvar cancer supports the notion that definitive chemo-radiotherapy is an effective treatment for anogenital SCC [189]. In a single study in six node-positive SCC penile cancer patients, 4 of the 6 patients were recurrence-free and two had developed recurrence, of which one patient died [189]. In a currently unpublished observational cohort study in 40 loco-regionally advanced penile cancer patients fit for chemo-radiotherapy and treated with curative intent, Ottenhof and colleagues observed that only half of the patients proceeded to surgery, and one- and 2-year PFS was 32% with a > grade 3 toxicity rate of 40% [190]. Their regimen consisted of integrated boost intensity modulated radiotherapy with a dose of 59.5 Gy to the primary tumour in fractions of 1.8 Gy with mitomycin C on day one and capecitabin on radiation days. In comparison to peri-operative chemotherapy studies, the omission of surgery is a potential advantage of chemo-radiotherapy. As this strategy has only been evaluated in a single observational study without a published full text at the moment of writing, no recommendation can be made supporting this approach in patients suitable for other options.

6.1.4 Local recurrence after organ-sparing surgery

A second organ-sparing procedure can be performed if there is no corpus cavernosum invasion [136, 149, 191-193]. For large or high-stage recurrence, partial or total amputation is required, unless unresectable or concurrent with nodal or distant metastatic recurrence (see respective sections).

6.1.5 Summary of evidence and guidelines for local treatment of penile carcinoma

Summary of evidence	LE
Penile intra-epithelial neoplasia progress to invasive lesions in 2.6–13% despite treatment.	3
Response and recurrence rates of topical therapies for PeIN are 40–100% and 20% for IQ and 48–74% and 11% for 5-FU. For laser therapy, response rates are 52–100% and recurrence rates 7–48%. For glans resurfacing, recurrence rates are as low as 4%.	3
A SR including retrospective studies on organ-sparing surgical treatment of the primary lesion shows that cumulative mean 5-year RFRs are 82% in case series and 76.7% in non-RCTs. For (partial) amputative surgery these are 83.9% in case series and 93.3% in non-controlled studies. The cumulative mean 5-year RFR was 69.4% for patients treated with laser therapy for invasive disease.	3
Current literature on frozen section analysis in organ-sparing surgery is heterogeneous and conflicting.	3
Tumour distance to the resection margin < 1 mm resulted in higher local recurrence rates in a recent large retrospective case series from a tertiary referral centre.	3
Several retrospective series from claims databases and high-volume centres studying non-specified organ-sparing surgical and ablative techniques show no impact of local recurrence on CSS where case mix is pitched towards lower grade, lower stage tumours. However, a recent large retrospective series of glansectomies performed in high-volume centres showed local recurrence was a predictor of poor CSS in a cohort with a high number of T2, T3 and high-grade lesions.	3
The cumulative mean 5-year RFRs are 78.6% after brachytherapy and 55.2% after EBRT.	3
For neo-adjuvant chemotherapy, pooled ORR was 53% (95% CI: 42–64%), the pCR rate in prospective studies was 4–10% (95% CI: 5–30%) in a recent SR and meta-analysis.	2a

Recommendations	Strength rating
Offer a balanced and individualised discussion on benefits and harms of possible treatments options with the goal of shared decision making.	Strong
Inform patients of the higher risk of local recurrence when using organ-sparing treatments compared to amputative surgery.	Strong
Topical therapy	
Offer topical therapy with 5-fluorouracil or imiquimod to patients with biopsy-confirmed penile intra-epithelial neoplasia (PeIN).	Weak

Clinically assess treatment effects after a treatment-free interval and in cases of doubt perform a biopsy. If topical treatment fails, it should not be repeated.	Weak
Laser ablation	
Offer laser ablation using CO_2 or Nd:YAG laser to patients with biopsy-confirmed PeIN, Ta or T1 lesions.	Weak
Organ-sparing treatment: surgery (circumcision, wide local excision, glansectomy and glans resurfacing)	
Offer organ-sparing surgery and reconstructive techniques to patients with lesions confined to the glans and prepuce (PeIN, Ta, T1–T2) and who are willing to comply with strict follow-up.	Strong
Perform intra-operative frozen section analysis of resection margins in cases of doubt on the completeness of resection.	Weak
Offer salvage organ-sparing surgery to patients with small recurrences not involving the corpora cavernosa.	Weak
Organ-sparing treatment: radiotherapy (EBRT and brachytherapy)	
Offer radiotherapy to selected patients with biopsy-confirmed T1 or T2 lesions.	Strong
Amputative surgery (partial- and total penectomy)	
Offer partial penectomy, with or without reconstruction, to patients with invasion of the corpora cavernosa (T3) and those not willing to undergo organ-sparing surgery or not willing to comply with strict follow-up.	Strong
Offer total penectomy with perineal urethrostomy to patients with large invasive tumours not amenable to partial amputation.	Strong
Offer amputative surgery to patients with large local recurrences or corpora cavernosa involvement.	Weak
Multimodal therapy	
Offer induction chemotherapy followed by surgery to responders, or chemo-radiotherapy to patients with non-resectable advanced primary lesions, or to patients with locally advanced-disease who refuse surgical management.	Weak

6.2 Regional lymph node management: clinically evident disease (cN1–cN3)

6.2.1 Introduction

The development of lymphatic metastases in penile cancer follows the route of anatomical drainage from the primary tumour to the superficial and then deep inguinal LNs (which can occur on both or either side), followed by the ipsilateral pelvic LNs. The superficial nodes are located under the subcutaneous fascia and above the fascia lata within Scarpa's triangle. The deep nodes lie within the region of the fossa ovalis where the superficial saphenous veins anastomose with the femoral vein at the saphenofemoral junction. The Cloquet's node (or Rosenmuller's node) is located medial to the femoral vein around the entrance to the femoral canal and marks the transition between inguinal and pelvic regions. Daseler et al., divided the superficial inguinal LNs into five regions centred around the saphenofemoral junction; central, lateral superior, lateral inferior, medial superior and medial inferior [194]. Studies of radical ILND (rILND) as well as single-photon emission computed tomography (SPECT) imaging suggest that sentinel inguinal nodes, i.e., those first affected by lymphatic spread, appear to be located in the medial superior zone followed by the central inguinal zones [194-196].No solitary lymphatic spread has been observed from the penis to the two inferior groin regions and no direct drainage to the pelvic nodes, either [194-196].

Pelvic nodal disease does not occur without ipsilateral inguinal LN metastasis. Also, crossover metastatic spread, from one groin to the contralateral pelvis, is rare [197]. Further lymphatic spread from the pelvic nodes to retroperitoneal nodes (para-aortic, para-caval) is classified as systemic metastatic disease [198].

The management of regional LNs is decisive for patient survival. The presence and extent of nodal involvement is singulary the most important prognostic factor in patients with penile cancer. Cure can be achieved in limited LN-disease confined to the regional LNs. Radical LND is the treatment of choice. Multimodal treatment combining surgery, chemotherapy, or radiotherapy is often indicated for more advanced disease.

In clinically positive LNs (cN1/cN2), more extensive LN metastasis is highly likely and LN surgery with histology is required. Given the very high chance of recurrence, enlarged fixed inguinal LNs (cN3) or clinically evident pelvic metastases require multimodal treatment by induction chemotherapy and consolidative surgery in responding patients. Even if present in only one node, extra-capsular extension/ENE, or pelvic LN metastasis found at surgery carries a high risk of progression and is classified as pN3 and requires multimodal treatment.

Given the complexities of regional node management, the intent of the Panel in the following sections (i.e., Sections 6.2–6.4) is to describe the available evidence-based strategies in the management of clinically evident LN metastases (i.e., cN1–cN3). These include inguinal/pelvic LND, chemotherapy, radiotherapy ± chemotherapy and integrated strategies such as neoadjuvant and adjuvant therapies combined with surgery. The reader is encouraged to review the text sections, summaries of evidence, and recommendation tables collectively in order to better understand recommendations for single vs. multimodal treatment and currently available data utilising various strategies.

*6.2.2 **cN1–N2 disease: radical inguinal lymph node dissection***

6.2.2.1 Indication for radical inguinal lymph node dissection

Radical ILND remains the standard of care for patients with cN1–2 (or cN0 patients with a tumour positive SN at DSNB). In low-volume disease (pN1) rILND is curative with a suggestion of equivalent outcomes in those patients without nodal disease [199-201].

Despite this, several studies have demonstrated continuing non-adherence to accepted international guidance [202-205]. Cindolo *et al*., evaluated adherence of twelve European and American centres to the EAU recommendations [205]. They reported a 26.3% rate of non-adherence in terms of LN management. For those patients managed as per guidance with LND there was a statistically significant association with OS (adjusted HR: 0.48; 95% CI: 0.24–0.96, p = 0.038) [205].

6.2.2.2 What is an acceptable definition?

Daseler's original description of a rILND in 1948 is considered the classical description of a radical inguinal LN dissection (rILND) (see Table 6.1) [194]. Despite this, considerable variation exists across high-volume centres. In an international survey of surgeons' practice in European high-volume centres, consensus was not found in the definition of the superior and lateral borders of the dissection, and whether the fascia lata and saphenous should be preserved [206]. This variation in practice is likely a reflection of clinicians and patients desire to reduce the significant burden of morbidity acknowledged in the literature associated with rILND (see later section on complications). A SR of the literature by the Panel identified only one other description of a modified template used in clinical N1–2 disease by Yao et al. [207] (see Table 6.1). This retrospective cohort study of 201 fascial-sparing inguinal dissections (fsILND) with < N2 disease, demonstrated comparable oncological outcomes to rILND with 3-year DFS of 92.1% (100% for pN0, 91.3% for pN1, 80% for pN2, and 33.3% for pN3 disease, respectively) and a complication rate of 29.3%. To date, however, no direct comparison exists between rILND and fsILND in this group of patients (Table 6.1).

Table 6.1: Variations in radical inguinal lymphadenectomy

	Superior	Lateral	Medial	Inferior	base	Fascia preserved	Saphenous spared	Sartorius transposition
rILND [194]	Superior margin of external ring to the anterior superior iliac spine	Anterior superior iliac spine inferiorly 20 cm	15 cm downwards from the pubic tubercle	Apex of femoral triangle	Sartorius, femoral vessels, adductor longus	No	No	Yes
fsILND [207]	Superior margin of external ring to the anterior superior iliac spine	Anterior superior iliac spine inferiorly 20 cm	15 cm downwards from the pubic tubercle	Apex of femoral triangle	Fascia	Yes. Deep inguinal LNs, medial to the femoral vein, dissected just distal to the fossa ovalis	Yes	No

fsILND = fascia-sparing inguinal lymph node dissection; RILND = radical inguinal lymph node dissection.

6.2.2.3 Quality metrics

To standardise the quality of resections, several studies have attempted to look for surrogate markers to infer complete oncological resection including LN yield (LNY), LN density (LNDen), and time to completion of surgery.

6.2.2.3.1 Lymph node yield and density

In a SR commissioned by the Panel, several studies were identified examining the association between LNY/LNDen and survival as a surrogate marker of adequate dissection in penile cancer [203, 208-212]. However, LNY varied from ≥ 8 to ≥ 15–16 and LND ≤ 6.7 to ≤ 22%. The variance in accepted values is likely because of different surgical templates, variable pathological assessment, and stage migration. Consequently, widespread adoption of LNY and LNDen as a predictor of survival and as quality markers cannot be recommended.

6.2.2.3.2 Timing of surgery

Several studies have highlighted the importance of expedient LN management in patients with cN0 disease vs. surveillance with LND on presentation of clinical disease. Two non-RCTs have demonstrated a survival benefit in patients who underwent early ILND compared with delayed ILND (within six weeks of primary surgical treatment vs. surgery following identification of positive nodes during surveillance), showing 3-year CSS 84% vs. 35% (p = 0.0017) and 3-year CSS 71% vs. 50%, respectively [98, 213].

The evidence in pN1–2 regarding optimal timing of LN management is limited. Chipollini *et al*., examined the effects of early vs. late inguinal LN dissection (> three months following primary surgery) in 84 patients with cN0 and cN+ disease. Overall, those patients undergoing early ILND demonstrated a 5-year DSS of 64.1% vs. 39.5% for late dissection with an unadjusted HR of 0.66 (0.32–1.37). However, when sub-analysis was performed in cN+ patients, the 5-year DSS for early vs. late dissections failed to delineate a statistically significant benefit (31.8% vs. 35.3%, respectively) [214].

Gulia *et al.*, examined 28 patients undergoing rILND stratified by < 6 months (group 1) and more than 6 months (group 2) from treatment of the primary tumour (70% and 50% palpable at presentation, respectively). The 5-year CSS was 91 and 13%, respectively (p = 0.007) [215].

6.2.2.4 Complications

Radical ILND carries a significant morbidity due to impaired lymph drainage from the legs and scrotum, however it can be lifesaving and therefore should not be avoided [216].

Historical morbidity of the procedure has been as high as 61% [217]. Contemporary large series of rILND suggest between 21–55% of men will suffer a complication [115, 218, 219]. The reduction in morbidity is likely due to a better understanding of pre-, intra-, and post-operative management (see Table 6.2). In a SR commissioned by the Panel the most reported complications in recent series were wound infections (2–43%), skin necrosis (3–50%), lymphoedema (3.1–30%), lymphocele formation (1.8–26%), and seroma (2.4–60%) [115, 199, 215, 218-225]. Table 6.2 lists several strategies and conditions associated with increase, decreased or uncertain effects on morbidity outcomes reported in penile cancer, urologic or in other cancers. Future studies specific to ILND and strategies to decrease morbidity are needed.

Table 6.2: Impact of pre-intra- and post-operative factors on morbidity following radical inguinal lymph node dissection

Positive impact	Negative impact	Uncertain benefit
Linear transverse incision [226, 227]	S-shaped incision, vertical incision [217, 226, 228]	Vacuum dressings [229]
Saphenous sparing [227, 230, 231]	Time-controlled drainage [232]	Fibrin glue [233]
Volume-controlled drainage [232]	Ultrasonic device [234]	Advanced bipolar device [235]
Fascial sparing [207]	Sartorius transposition [219]	
Minimally-invasive techniques [236-238]	Raised BMI [219]	
Lymphoedema prevention, e.g., massage, skin care, saphenous vein-sparing surgery [227, 239]	Increased disease burden [115]	
Deep venous thrombosis prophylaxis [240]	Sarcopenia [220]	
Prevention of surgical site infections, e.g., prophylactic antibiotics, shaving, skin prep [241]		

6.2.2.5 Open versus minimally-invasive approach

In recognition of the significant morbidity associated with rILND, clinicians have sought to reduce these through technical modifications. Expanding interest and experience in minimally-invasive techniques have led to the introduction of video-endoscopic inguinal LND (VEIL) and subsequently robot-assisted video-endoscopic inguinal LND (RAVEIL), using rILND or fsILND templates.

Ports are generally placed at the apex of the femoral triangle, although variations include lateral and hypogastric approaches allowing pelvic lymph node dissection (PLND) through the same incisions [242-244].

A review of the literature commissioned by the Panel identified a single incomplete RCT in 2012 which closed prematurely due to poor accrual, with patients preferentially choosing minimally-invasive approaches over open [245]. The remaining studies identified were either retrospective cohort- or comparative series. Narrative review would suggest that although operative time is longer, LN yields can be similar to open ILND, length of hospital stay shorter in VEIL/RAVEIL and wound complications lower, though lymphocele and readmission rates were equivalent [113, 236, 238, 246-248].

Follow-up for the minimally-invasive approaches were short, and there was a high proportion of patients receiving VEILND or RAVEIL as prophylaxis as opposed to clinically node-positive disease, precluding incorporation in the current guidance. In addition, some studies where open rILND was used as a comparator, involved more morbid manoeuvres when using an open approach, such as Sartorius transposition and saphenous vein sacrifice, which were not replicated in minimally-invasive procedures.

6.2.2.6 Summary of evidence and guidelines for radical inguinal lymph node dissection in cN1-2 disease

Summary of evidence	**LE**
Open radical ILND is the standard for cN1–2 disease.	2a
Radical inguinal lymph node dissection carries a significant risk of complications (21–55%).	2a
A single study reported on fsILND, fascial-sparing ILND has been reported (single study) and in cN1–2 disease which appears to offer similar oncological outcomes, and reduced complications.	2b
Lymph node yield and LND appear related to survival, however, variance in accepted values, pathological assessment, and stage migration prevent recommendation of a specific LN count.	2a
Delay in nodal management of more than three to six months may affect DFS.	3
Minimally-invasive approaches for ILND (VEIL/RAVEIL) generally have longer operative times, equivalent LN yields, shorter length of hospital stay and lower wound complications when compared with open ILND. However, since current evidence is very limited in cN1–2 patients, no recommendation for minimally-invasive approaches can be provided.	2b

Recommendations	**Strength rating**
In patients with cN1 disease offer either ipsilateral: • fascial-sparing inguinal lymph node dissection (ILND) • open radical ILND; sparing the saphenous vein, if possible	Strong
In patients with cN2 disease offer ipsilateral open radical ILND; sparing the saphenous vein, if possible.	Strong
Offer minimally-invasive ILND to patients with cN1–2 disease only as part of a clinical trial.	Strong
Offer neoadjuvant chemotherapy as an alternative approach to upfront surgery to selected patients with bulky mobile inguinal nodes or bilateral disease (cN2) who are candidates for cisplatin and taxane-based chemotherapy (see Section 6.4.1).	Weak
Complete surgical inguinal and pelvic nodal management within three months of diagnosis (unless the patient has undergone prior neoadjuvant chemotherapy).	Weak

6.2.3 ***Prophylactic pelvic lymph node dissection***

Prophylactic PLND (pPLND) in most cases represents a staging procedure that can thus identify candidates for early adjuvant therapy, although in select patients may also provide a therapeutic benefit.

6.2.3.1 Indications for prophylactic pelvic lymph node dissection

6.2.3.1.1 Risk factors for pelvic nodal metastasis

To identify patients with pelvic LN metastasis in the absence of radiological evidence for LN involvement, several studies have tried to develop generalized estimating models based on inguinal characteristics using logistic regression and multivariate analysis. Among various predictors, the number of positive inguinal LNs (1–2 vs. 3, or more, with no extra-capsular extension) was associated with positive pelvic LNs in 0–6.5% of patients vs. 33–67% of patients [249, 250]. The presence of extracapsular spread was also consistently significantly associated with positive ipsilateral pelvic LN metastasis in 4 studies [249-252] Strong immunoreactivity of p53, LN density > 30% and primary tumour grade are also reported as predictors of pelvic LN involvement [250].

6.2.3.2 What is an acceptable dissection?

In a study by Yao *et el*., the authors prospectively mapped the distribution of positive pelvic LNs at the time of PLND in 128 patients [197]. Most patients underwent bilateral PLND (86.7%). The median number of nodes retrieved per groin was 18 (interquartile range [IQR] 10–30), with the distribution of positive nodes in the external iliac, obturator, common iliac, internal iliac and presacral packages 50%, 36.6%, 7%, 6.4% and 0%, respectively. Notably two patients were observed to have crossover metastasis from one inguinal region to the contralateral pelvic region, defying the accepted understanding of the historical literature. When the extent of dissection was considered in context of overall- and RFS there was no statistically significant difference [197]. Similar data was seen in a study by Zhu *et al*., with the external iliac package being more commonly involved than the obturator and common iliac packages [253].

To evaluate the prognostic impact of LN yield on survival outcomes for penile SCC, Chipollini *et al.*, examined 198 patients undergoing PLND [208]. In their cohort they found a LN yield of ≥ 9 was a predictor of RFS (HR: 0.53, p = 0.032).

6.2.3.3 Survival and recurrence

The evidence that pPLND has an additional therapeutic effect over surveillance or adjuvant radiotherapy (see Section 6.4.2.2) is limited and significant controversy remains. Djajadiningrat *et al*., estimated the 5-year DSS in all patients treated with pPLND was 51%. Patients with positive pelvic nodes had a significantly worse 5-year DSS than those without pelvic involvement (17%, 95% CI: 6–47 vs. 62%, 95% CI: 50–76, p < 0.001) [251]. A retrospective multicentre study compared the outcomes of bilateral pPLND for N2 or N3 disease vs. no surgery and reported better 5-year OS in the pPLND group (35% vs. 25%) without reaching statistical significance [254]. In N2 patients, 3-year OS was significantly better in the PLND group as compared to the no-surgery group (83.3% vs. 50.2%, p = 0.03) [254]. This difference was not evident in N3 patients.

6.2.3.4 Complications

There is limited data available regarding the reporting of complications from PLND. This is complicated by the fact that most patients will have already undergone a rILND which carries a significant morbidity as discussed above. A single-centre experience of 89 patients, undergoing open PLND for penile cancer reported an overall complication rate of 18%. Nine patients had wound complications including infection, seroma, and dehiscence. The remaining 5 patients had non-wound-related complications such as pneumonia, delirium, and ileus [251].

6.2.3.5 Minimally-invasive versus open pelvic lymph node dissection

In a SR commissioned by the Panel there were no reported studies that examined the role of minimally-invasive pPLND in the setting of penile cancer and PLND. There is, however, a significant body of evidence that exists in other common urological malignancies that demonstrates equivalent oncological outcome as well as improved morbidity profile and recovery profile.

6.2.3.6 Summary of evidence and guidelines for prophylactic pelvic lymph node dissection

Summary of evidence	**LE**
Prophylactic PLND in most cases represents a staging procedure that can thus identify candidates for early adjuvant therapy, although in select patients it may also provide a therapeutic benefit.	3
Three or more positive inguinal nodes or extranodal extension of cancer in inguinal nodes are associated with a significantly higher incidence of pelvic LN metastases.	3

Recommendations	Strength rating
Offer open or minimally-invasive prophylactic ipsilateral pelvic lymphadenectomy to patients if: • three or more inguinal nodes are involved on one side on pathological examination • extranodal extension is reported on pathological examination	Weak
Complete surgical inguinal and pelvic nodal management within three months of diagnosis (unless the patient has undergone neoadjuvant chemotherapy).	Weak

6.3 Clinical N3 disease (cN3)

*6.3.1 **Diagnostic evaluation***

Patients with clinical N3 disease as defined by the presence of a fixed inguinal mass (i.e., to skin or underlying structures) or pelvic lymphadenopathy based upon imaging should undergo a complete staging evaluation including cross sectional imaging (i.e., PET/CT or CT, see Section 5.2.3), if not already performed [255]. Biopsy of the inguinal mass in the setting of a patient with a known diagnosis of penile cancer is not required but should be performed in a previously undiagnosed patient, as needed, to establish the diagnosis and facilitate accurate staging.

*6.3.2 **Management strategy***

Neoadjuvant chemotherapy (NAC) is a reasonable strategy among cN3 patients based on the results of a recent SR which reported radiological response rates of approximately 53% and pathological complete response in approximately 12.8% of patients [187, 256]. This review consisted mostly of retrospective series; complete response rates in the intention to treat population were 10% (paclitaxel, ifosfamide, and cisplatin [TIP]) and 4% (docetaxel, cisplatin and fluorouracil [TPF]) in prospective trials [177, 180]. In responding patients, and those with no evidence of disease progression, surgical resection to remove all residual disease utilizing radical inguinal and PLND techniques is the preferred strategy. For a detailed examination of peri-operative chemotherapy please see Section 6.4.1.

Pre-operative radiotherapy was used in a single study among a cN3 cohort of 12 patients and reported an objective response in only 2 patients with 7 of 12 patients subsequently undergoing ILND. Only 2 patients (17%) survived 5 years [257]. It is worth recognising that this data, however, utilises historical radiotherapy techniques precluding meaningful extrapolation to modern practice (see Section 6.4.2 for further details).

Surgery as the initial treatment in patients with a fixed inguinal mass or clinically evident pelvic adenopathy (cN3) at presentation or recurrence is discouraged in routine management. While often technically feasible a “surgery first approach” often results in large skin/soft tissue defects, the need for myocutaneous flap reconstruction, prolonged hospital stays (mean or median 8.5–23 days) and is associated with high overall complication rates (65–77%) [258, 259]. In a single-centre study among 24 patients treated with surgical debulking alone in the advanced disease setting, the median CSS and DFS were only six and three months, respectively [259]. In the same study 17.5% of patients exhibited rapid progression of disease post-surgery and never received adjuvant therapy [259].

*6.3.3 **Patient selection for consolidative radical inguinal/pelvic lymphadenectomy***

Patients whose tumours respond to NAC and subsequently undergo surgical consolidation represent a favourable subgroup of patients with a mean 5-year survival of 56.9% according to a SR [256]. Among cN3 patients who are not candidates for conventional multi-agent chemotherapy, pre-operative chemo-radiation/radiation can be offered in an attempt to downsize tumours to improve resectability. The evidence for this, however, is recognised to be weak but is being prospectively investigated in the InPACT study [260].

*6.3.4 **Surgical technique***

6.3.4.1 Inguinal lymph node dissection

Surgical resection should proceed 5–8 weeks after completion of chemotherapy to provide time for haematologic recovery and other therapy related symptoms to improve.

Pre-operative planning to remove all residual disease taking into consideration the size of the mass, involvement of surrounding structures, and the anticipated skin and soft tissue defects as well as plastic surgical consultation (as appropriate) is required for successful outcomes.

6.3.4.2 Lymphadenectomy boundaries

Surgical boundaries should follow that of a ‘radical inguinal lymph node’ dissection” (described in Table 6.1). Wide resection of involved skin is often required with *en bloc* ILND. Considering the extent of inguinal

metastases along with fixation to adjacent structures, minimally-invasive techniques (i.e., robotic-, laparoscopic ILND) are considered inappropriate in cN3 inguinal metastases.

6.3.4.3 Pelvic lymph node dissection

Simultaneous PLND should be performed at the time of ILND if pelvic LN metastases were clinically evident at diagnosis. Ipsilateral PLND should also be performed in a simultaneous (preferred) or delayed fashion in the setting of advanced bulky inguinal metastases without clinically evident pelvic metastases as well (i.e., prophylactic). In the latter setting, microscopic pelvic metastases were noted quite frequently (44–100%) in the setting of extracapsular disease and especially when an inguinal mass was present in one series [249].

6.3.4.4 Surgical complications in cN3 disease

Resection of bulky/fixed inguinal masses with or without prior chemotherapy is associated with a variety of complications. Minor complications not requiring hospitalization or surgical intervention are common and tolerable when cure or significant palliation can be achieved. Major post-surgical complications requiring medical or surgical intervention or associated with disability, or death, in several series included infection/sepsis (1.5–4.5%), lymphocele requiring drainage (0–3.8%), wound dehiscence or necrosis requiring debridement (1.5–5.6%), pneumonia (0–2.9%), deep venous thrombosis/pulmonary embolus (0–8.7% and death (0–5.6%) [180, 258, 259]. Overall, in the three selected series of patients treated at experienced centres the incidence of major complications as described above was less than one in ten patients with 3/82 (3.9%) patients succumbing to sepsis or other early peri-operative complications.

*6.3.5 **Summary of evidence and guidelines for the surgical management of cN3 disease***

Summary of evidence	**LE**
Surgery alone will rarely cure patients with cN3 disease.	3
Even when technically feasible, upfront surgery is associated with significant complications which may delay or prevent delivery of adjuvant therapy.	3
About half of the patients with advanced (cN2–cN3) penile cancer respond to combination chemotherapy. Responders that subsequently undergo consolidative inguinal/PLND have an OS chance of about 50% at 5 years.	2a
Inguinal LND in cN3 patients often requires resection of overlying skin to effectively remove a fixed bulky nodal mass.	4
The available literature includes virtually no cN3 patients to assess the efficacy or safety of minimally-invasive ILND.	4

Recommendations	**Strength rating**
Offer neoadjuvant chemotherapy (NAC) using a cisplatin- and taxane-based combination to chemotherapy-fit patients with pelvic lymph node involvement or those with extensive inguinal involvement (cN3), in preference to up front surgery. (see Section 6.4.1).	Weak
Offer surgery to patients responding to NAC in whom resection is feasible.	Strong
Offer surgery to patients who have not progressed during NAC, but resection is feasible. See also (chemo)radiation.	Weak
Do not offer Video Endoscopic Inguinal lymphadenectomy.	Strong

6.4 Role of multimodal chemotherapy/radiotherapy in the management of (regional) lymph nodes

*6.4.1 **Systemic therapy***

6.4.1.1 Neoadjuvant chemotherapy

Bulky inguinal LN enlargement indicates extensive lymphatic metastatic disease for which few patients will benefit from surgery alone. Neoadjuvant chemotherapy before inguinal LN surgery allows for early treatment of systemic disease and down-sizing of the inguinal LN metastases. In responders, complete surgical treatment is possible with reasonable clinical outcome.

Cisplatin/5-FU (PF) chemotherapy achieved a response rates of 25–50% with acceptable toxicity [261, 262]. Over a period of 30 years, five different NAC regimens including PF were used in twenty patients, with long-term survival in 37% of responders who underwent radical LN surgery after NAC [263]. In the EORTC 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 (pCRs) [186].

Hypothetical 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. A phase II trial evaluated treatment with 4 cycles of neoadjuvant paclitaxel, cisplatin, and ifosfamide (TIP) in patients with clinical N2 or N3 LN metastases [180]. An objective response rate (ORR) of 50% was reported in 30 patients, including three pCRs. The estimated median time to progression (TTP) was 8.1 months and the median OS was 17.1 months. Long-term DFS was observed in 67% of responding patients and 7% of non-responding patients.

The combination of PF plus a taxane has been used in neoadjuvant and adjuvant settings [183, 184, 264, 265]. A phase II trial with docetaxel, cisplatin, and 5-FU (TPF) reported an objective response of 38.5% in 29 locally-advanced or metastatic patients, although the study did not meet its primary endpoint, and there was significant toxicity [184]. A prospective study testing neoadjuvant TPF in 26 patients with loco-regionally advanced penile cancer showed a pathologic complete response in one patient, with a 2-year PFS and DSS probability of 12% and 28%, respectively [177]. Treatment was discontinued in 23% of patients because of toxicity. In a recent meta-analysis analysing 10 studies (n = 182 patients, mostly retrospective), the pooled ORR was 53% (95% CI: 42–64), and the overall mortality was 55% (95% CI: 40–70) [187]. The available evidence favours a cisplatin- and taxane-based combination (doublet or triplet) as the preferred approach.

Overall, these results support the activity of pre-operative chemotherapy in patients with clinically-involved regional LNs from penile SCC. However, randomised studies are lacking and substantial concerns remain regarding the selection of patients who are best suited for a systemic therapy approach upfront. A large retrospective study including 743 patients who received a LND from several international institutions suggested patients with a clinical N3 stage constituted the cohort with the most appreciable benefit from NAC use, compared to LND alone [266]. Bilateral inguinal LN involvement emerged as a strong negative predictor of clinical outcome in patients with penile SCC, together with pelvic nodal involvement.

In summary, given the poor outcome of upfront surgery, NAC is a potentially-suitable approach for patients having pelvic LN (cN3) metastases or fixed inguinal LN involvement (cN3), or bulky or bilateral involvement (cN2). In nonresponding patients, the potential benefits of surgery should be re-evaluated as prognosis is poor in these patients. See also section on chemo-radiotherapy.

6.4.1.2 Adjuvant chemotherapy

There are known poor prognostic characteristics for a subset of patients with resected high-risk disease (such as involved pelvic LNs), indicating the likely presence of micrometastatic disease. Data exists on response rates for those with metastatic disease and there is possible benefit for pre-operative chemotherapy for those with unresectable locally advanced disease as described above. With extrapolation from other diseases, it stands to reason that systemic therapy following resection (i.e., adjuvant therapy) may improve outcomes.

A retrospective multicentre analysis of patients with resected pathologically involved pelvic LNs suggested a potential benefit of adjuvant chemotherapy [264]. In this series, 84 patients were analyzed. Patients who received chemotherapy for relapsed disease were excluded. Compared to those not receiving adjuvant chemotherapy, patients who received adjuvant chemotherapy were younger, had lower T stage, more likely to have unilateral (rather than bilateral) LN involvement, and were less likely to receive adjuvant radiation. On multivariable analysis, receipt of adjuvant chemotherapy was associated with improved OS (HR: 0.40, 95% CI: 0.19–0.87, p = 0.021). Additional series have also been reported, including a series of 611 patients from the National Cancer Database reported in abstract form [267]. After adjusting for co-variates, there was no difference in survival for those receiving adjuvant chemotherapy.

A recent meta-analysis examined this issue. After a systematic search, 7 studies were identified examining the use of peri-operative chemotherapy, 4 of which examined adjuvant chemotherapy (n = 771) [268]. There was no difference in survival for those receiving adjuvant chemotherapy vs. observation (HR: 0.95, 95% CI: 0.48–1.80).

Upon examination of the overall data, there is no strong data supporting the use of adjuvant chemotherapy to improve OS following surgical resection of the primary tumour and involved LNs. However, given the fact that RFS is a relevant endpoint that has been suboptimally studied and there is a subset of patients at very high risk of recurrence, the Panel recommends a balanced discussion of risks and benefits of adjuvant chemotherapy

in those thought to be healthy candidates. As previously stated for the neoadjuvant setting, the benefit from adjuvant chemotherapy is expected to be highest in the population of patients with pathological N3 stage, in particular for those patients with pelvic nodal involvement [266]. See also Section 6.4.1.2 on adjuvant radiation and chemo-radiotherapy.

6.4.1.3 Summary of evidence and guidelines for neoadjuvant and adjuvant chemotherapy

Summary of evidence	**LE**
Results support the activity of NAC in patients with clinically involved regional LNs from penile SCC. However, randomised studies are lacking, and substantial concerns remain regarding the selection of patients who are best suited for a systemic therapy approach upfront.	2b
The available evidence favours a cisplatin- and taxane-based combination (doublet or triplet) as the preferred approach.	2b
Limited data support the use of adjuvant chemotherapy to improve OS following surgical resection. However, it could be offered to patients with pN3 disease post-LND if NAC has not been received, upon careful consideration of risks and benefits with the patient.	4

Recommendations	**Strength rating**
Offer neoadjuvant chemotherapy using a cisplatin- and taxane-based combination to chemotherapy-fit patients with pelvic lymph node involvement or those with extensive inguinal involvement (cN3), in preference to up front surgery.	Weak
Offer chemotherapy as an alternative approach to upfront surgery to selected patients with bulky mobile inguinal nodes or bilateral disease (cN2) who are candidates for cisplatin and taxane-based chemotherapy.	Weak
Have a balanced discussion of risks and benefits of adjuvant chemotherapy with high-risk patients with surgically resected disease, in particular with those with pathological pelvic LN involvement (pN3). See also section on post-operative radiotherapy.	Weak

*6.4.2 **Radiotherapy***

6.4.2.1 Pre-operative radiation therapy

The role of pre-operative chemo-radiotherapy is being investigated in the ongoing InPACT trial [260]. Since surgical therapy of enlarged LNs is of paramount importance, it is unlikely that pre-operative radiotherapy alone would provide sufficient benefit. Should a patient who is otherwise unfit for chemotherapy require treatment to LNs while awaiting surgery, radiotherapy alone may be considered using conventional daily fractionation to 45–50Gy. Radiotherapy to the groins in penile cancer conceptually requires inclusion of the pre-pubic fat a in order to cover in transit lymphatics [269].

6.4.2.2 Post-operative radiation therapy

Adjuvant radiation therapy for node-positive penile cancer remains controversial. Since there is no level 1 evidence to support the benefit of radiation therapy in terms of disease recurrence and survival, it is not recommended in prior guidelines [270, 271]. Radiotherapy is being used in some institutions in the management of regional LNs for penile SCC, based on evidence and experience with other SCC sites (such as head/neck and vulvar carcinomas) [174, 272, 273].

Jaipuria *et al*., reported that following inguinal- and pelvic LND, patients with > 2 positive LNs but negative pelvic nodes (n = 32) had increased OS with adjuvant radiation therapy compared to adjuvant chemotherapy (48 months vs. 14 months $p < 0.0001$) [274]. Although 68% of patients had ENE, there were no in-field failures. The radiation dose was higher than that commonly used under these circumstances, 54 Gy for ENE and up to 57–60 Gy for gross residual disease. With a lower radiation dose of 50 Gy, Johnstone *et al.*, reported a high rate of in-field failures (32/39) [275]. At this dose, adjuvant radiation therapy (either groin: $p = 0.016$ or inguinal-pelvic: $p = 0.006$) improved RFS only for patients *without* ENE. Ager *et al*., reporting on the experience with pN3 disease (either ENE or pelvic LN+) in two tertiary referral centres in the UK also found dose to be critically important [276]. A 121 of 146 patients received adjuvant radiotherapy. The 5-year RFS was 51%. Twenty-six of 55 recurrences were in-field, but the risk of in-field failure was twice as high for lower doses < 50 Gy.

For 92 patients with positive pelvic LN from 4 international centres, adjuvant radiation was found to prolong DSS by 6 months and delay the time to recurrence [277].

The data collated in Table 6.3 reveal variable results with conventional radiotherapy delivered in the adjuvant setting, potentially impacted by HPV status and presence/absence of ENE. Also notable in the data is the fact that traditional radiotherapy doses delivered to microscopic disease may be insufficient. Recent genomic data analyses have modelled that a higher radiation dose may be necessary for management of penile cancer primary lesions and nodal basins [278, 279].

Table 6.3: Adjuvant conventional radiotherapy for node-positive penile cancer

Author	n	stage	aRT	Adj CT	RT	LR	OS	Study type
Jaipuria 2020 [274]	45	anyT pN2-3 pelvis pN-	25	7	VMAT/IMRT, 45 Gy basic, 54 Gy ENE, 57-60 macro	No InF	47 mo. RT vs. 14 mo. CT	Prosp registry
Johnstone 2019 [275]	93	anyTpN3 ENE- ENE+			50/25 no details		↑OS aRT p = 0.037 or aCT p = 0.038 ↑DSS aRT p = 0.04	4 centres
Winters 2018 [280]	136	pT1-3 pN1-2			45 Gy + boost 45%		↑OS aRT 5 yr. 64% vs. 53%	NCDB
Tang 2017 [277]	92	N3 +pelvis	40		63% 50/25, 13% > 50 Gy		↑OS aRT 12.2 vs.8 P=0.04 ↑DSS 14.4 vs.8 p = 0.02	4 centres
Ager 2021 [276]	146	pN3 (ENE or pelvis+)	121		45/20 to 54/25 2X↑LR if < 50	26 inF	OS 44% RFS 5y 51%	2 centres UK
Bandini 2021 [34]	507	ILND	86 HPV+ 40 aRT				↑OS aRT p = 0.015 Also propensity matched analysis	11 centres

ADj = adjuvant; aRT = adjuvant radiotherapy; CT = chemotherapy; ENE = extra-nodal extension; HPV = human papillomavirus; ILND = inguinal lymph node dissection; mo = month; n = number of patients; NCDB = National Cancer Database; OS = overall survival; RFS = recurrence free survival; yr = year.

HPV status could be a suitable selection factor for patients who will benefit from adjuvant radiotherapy after ILND (in analogy to other HPV-related cancers). Bandini *et al.*, reported on 507 patients from 11 centres, 86 of whom were HPV+. Among patients receiving adjuvant radiotherapy, those harbouring HPV-positive tumours appeared to have an increased OS relative to HPV-negative patients. However, more (prospective) studies are needed to validate these findings [34].

As in other SCC sites such as head and neck cancer, HPV status may also predict for increased responsiveness to combined chemo-radiotherapy. Yuan *et al.*, reported improved loco-regional control (LRC) of 83% over 38% (p = 0.038) for node-positive p16+ patients receiving chemo-radiotherapy following LND [273]. Twenty-eight of 51 patients were LN+, of whom 14 received chemo-radiotherapy, 7 of whom were HPV-positive. Overall, regardless of HPV status, 2-year LRC was 54% for those receiving adjuvant chemo-radiotherapy vs. 13% (p = 0.006). Choo *et al.*, found similar efficacy of adjuvant chemo-radiotherapy with improved CSS at one and 2 years, even though the patients selected for adjuvant chemo-radiotherapy had a higher number of positive LNs (64% > 5 vs. 8%),

more pN3 disease (72% vs. 17%) and more ENE (45% vs. 17%) [281]. The OS was the same for the unfavourable group receiving adjuvant chemo-radiotherapy as it was for the more favourable earlier-stage patients not receiving chemo-radiotherapy.

Although PLND is recommended for patients with high-risk groin pathology (N2–N3), this is not the practice in all jurisdictions. Maibom *et al.*, reported from Denmark on the use of inguinal-pelvic chemo-radiotherapy for 21 patients with a median follow-up of 74 months [282]. All patients had ENE and two-thirds had bilateral groin disease, with a median OS of 84 months and 57% 5-year survival. This concept is being tested in the currently accruing InPACT trial where men with high-risk groin pathology can be randomised to chemo-radiotherapy or PLND followed by chemo-radiotherapy [260].

6.4.2.3 Summary of evidence and guidelines for pre- and post-operative radiotherapy

Summary of evidence	**LE**
Adjuvant radiotherapy results in increased OS if greater than two inguinal LN-positive and PLND-dissection negative.	2b
Adjuvant conventional radiotherapy doses are often insufficient for durable control. Increased DSS and RFS in penile cancer requires 54 Gy for ENE and 57–60 Gy for positive margins.	3
Peri-operative chemo-radiotherapy	
chemo-radiotherapy significantly improves loco-regional control over radiotherapy alone for other SCC originating in anal canal or head and neck, whilst in vulvar cancers it improves OS. The evidence is, however, sparse in penile cancer.	1b

Recommendations	**Strength rating**
Offer adjuvant radiotherapy (with or without chemo sensitisation) to patients with pN2/N3 disease, including those who received prior neoadjuvant chemotherapy.	Weak
Offer definitive radiotherapy (with or without chemo sensitisation) to patients unwilling or unable to undergo surgery.	Weak
Offer radiotherapy (with or without chemo sensitisation) to cN3 patients who are not candidates for multi-agent chemotherapy.	Weak

6.5 Systemic and palliative therapies for advanced disease

6.5.1 Introduction

Much of our current standard of care for this rare disease has evolved based upon extrapolated experience with similar cancers. The most common regimens utilized today for advanced disease are similar to those routinely used in the peri-operative setting, consisting of platinum-based regimens. Most data come from institutional or retrospective studies, but cooperative groups have occasionally studied this disease via prospective phase II studies.

6.5.2 Chemotherapy

Phase II cooperative group studies with bleomycin, methotrexate, and cisplatin (BMP) and irinotecan cisplatin yielded response rates of 31–33% [186, 283]. The median OS for BMP was 28 weeks. Toxicity was a concern with both regimens, especially pulmonary toxicity from bleomycin.

A retrospective study of cisplatin and 5-FU (PF) presented a response rate of 32% and median OS of 8 months. Toxicity was manageable for this patient population [284].

Addition of taxanes to cisplatin-based regimens was associated with promising activity including CRs. Docetaxel, cisplatin, and fluorouracil (TPF) was prospectively studied in a cohort with distant metastasis (28%) or locally-advanced disease (72%). The response rate was 38.5% and median OS of 14 months; there were 2/26 patents with CR [184]. The study did not meet its efficacy endpoint and toxicity of TPF was a concern. Another prospective study of TPF in exclusively metastatic (M1) disease showed an objective response rate of 38.5% and median OS of 7 months [285]. The latter study did meet its efficacy endpoint and toxicity was interpreted as acceptable.

Paclitaxel, ifosfamide and cisplatin (TIP) was prospectively studied in patients with metastases confined to LNs (N2–3, M0), having a response rate of 50% in this select population and 3/30 with surgically verified CRs [180]. Toxicity was manageable in this setting, but there are limited data available for TIP in distant metastatic disease.

A SR of cisplatin-based chemotherapy outcomes with and without taxanes suggested a higher toxicity rate with taxanes, 49% vs. 26% [187].

Vinflunine single-agent chemotherapy was prospectively studied in patients with advanced disease who were not eligible for curative surgery or NAC. Patients were required to have ECOG performance status ≤ 2 and estimated glomerular filtration rate (GFR) ≥ 60 mL/min. Median age was 70 years with a 27% response rate and median OS of 8.4 months. Toxicity was manageable.

A retrospective study of paclitaxel single-agent chemotherapy as second line reported a response rate of 20% and median OS 23 weeks [286]. Two studies of various second-line systemic therapy regimens found median OS of 4.5 – 5.6 months [287, 288].

A retrospective study of 101 patients looked at the efficacy of chemotherapy as first-, second- and third-line treatment [287]. The median OS for first-line chemotherapy was 7.2 months and with best supportive care, two months. The second-line regimens in seventeen patients included paclitaxel/carboplatin (41%), cisplatin/capecitabine (12%), paclitaxel (12%), or other (36%). There were two objective responses (12%), three stable disease (18%) and seventeen with progressive disease (71%) as best response. Paclitaxel/carboplatin was also reported in adjuvant and neoadjuvant case series and was well tolerated [289, 290].

These data support the recommendation of platinum-based chemotherapy as the preferred approach to first-line palliative systemic therapy. Choices include triplet regimens (TPF, TIP) and doublets (PF, paclitaxel/carboplatin), where doublets appear to have less toxicity. Both TPF and TIP combine two neurotoxic drugs and are not appropriate for patients with pre-existing neuropathy or low GFR. Other comorbidities and functional status should be carefully considered when selecting a regimen. While data for paclitaxel/carboplatin in advanced penile cancer are limited, it is reasonable to extrapolate from its use as palliative treatment of squamous-cell cancers from other sites. An alternative approach is single-agent chemotherapy with vinflunine or a taxane.

Effective second-line palliative chemotherapy regimens are lacking. Second-line chemotherapy in multiple studies was associated with median OS of 6 months or less. This is an unmet need that also applies to patients with tumour recurrence after adjuvant or neoadjuvant chemotherapy.

6.5.2.1 Immunotherapy

Immune-based therapies such as immune-checkpoint blockade, HPV-directed vaccines and adoptive T-cell therapies have emerged as potential treatment options for advanced penile cancer [291]. Given the relatively high expression of PD-L1 in penile SCC, several trials in progress assess checkpoint inhibition in advanced disease. None of these anti-PD(L)1 monotherapy trials has been published thus far. Trials presented at conferences reported response rates of 14–17% [292, 293].

Basket studies testing combination therapies have included penile SCC patients. In a phase I-II study of nivolumab combined with cabozantinib, with or without ipilimumab, 3 penile SCC patients were included: one partial response (PR) and 2 stable diseases (SD) were reported [294]. In another study testing the combination of ipilimumab and nivolumab, 5 penile SCC were included reporting 2 patients having SD [295]. In general, inclusion of patients with advanced penile SCC after chemotherapy exposure into early-phase basket trials is highly recommended.

6.5.2.2 Targeted therapies

Beyond chemotherapy, currently limited additional systemic options exist. Specific actionable genetic alterations appear rare in this disease. Targeted therapy against epidermal growth factor receptor (EGFR) has been tested, similar to SCCs originating from other anatomical regions.

Evidence of sporadic activity of several EGFR inhibitors have been reported from a few small clinical studies or case-series [296-298]. Dacomitinib, an orally-available pan-HER inhibitor, was tested as monotherapy in a phase II study including patients with locally-advanced and distant metastatic penile SCC. Twenty-eight patients were included in this study, and the ORR was 32.1% with one patient benefiting with a complete response [299].

Despite PIK3CA gene alterations have been reported as the most frequently identified potentially 'actionable' genomic alterations in SCC of the pelvic region, no data currently support the use of selected targeted agents in this disease [300].

6.5.3 Role of radiotherapy in palliation

Radiotherapy is frequently necessary for palliation of penile cancer and should be customized for unique presentations as necessary: e.g., ulcerative fixed LNs or dermal lymphatic spread. While standard palliative regimens should be readily employed, providers should be aware that re-treatment may be necessary for durable disease control [301]. This radio-resistance in some cases has been noted [178].

With respect to chemoradiotherapy for large/inoperable primary tumors, large palpable nodes, or pelvic nodal involvement, a Dutch prospective trial of 33 patients (median age 64: IQR 54-73) was recently released [351]. A response rate of 73% and a complete response rate of 39% (evalutated by FDG-PET/CT) was noted after mitomycin C + capecitabine chemotherapy and 49.5-59.4Gy radiation. The 2-year overall survival was 46% and salvage surgery was feasible if required. Importantly, treatment toxicity was low compared to neoadjuvant chemotherapy (followed by surgery) [351].

6.5.4 Summary of evidence and guidelines for systemic and palliative therapies for advanced penile cancer

Summary of evidence	LE
Low-level data support the use of platinum-based chemotherapy as first-line systemic therapy in advanced disease.	3
Effective second-line palliative chemotherapy regimens are lacking. Second-line chemotherapy in multiple studies was associated with median OS of six months or less.	3
Initial phase II or basket studies assessed anti-EGFR therapy or checkpoint inhibition, as monotherapy or combination therapy, in advanced disease. Early evidence of promising clinical activity has been reported in patients with penile cancer.	2b

Recommendations	Strength rating
Systemic therapies	
Offer patients with distant metastatic disease, platinum-based chemotherapy as the preferred approach to first-line palliative systemic therapy.	Weak
Do not offer bleomycin because of the pulmonary toxicity risk.	Strong
Offer patients with progressive disease under platinum chemotherapy the opportunity to enroll in clinical trials, including experimental therapies within phase I or basket trials.	Strong
Radiotherapy	
Offer radiotherapy for symptom control (palliation) in advanced disease.	Strong

7. FOLLOW-UP AND QUALITY OF LIFE

7.1 Unmet needs

Penile cancer has a significant impact on QoL and unfortunately there remain many unmet needs to address (see Table 1.1 in Chapter 1) [2]. The physical changes, along with the psychological and emotional stress that men with penile cancer suffer requires recognition and professional support before, during and after treatment. Holistic patient support services delivered by a multi-disciplinary team as a routine part of surveillance and follow-up should be standard of care. Patients with cancer endorse of the need for 'adjustment' and dealing with the 'new normal' as part of survivorship [302]. The extent of this and the time it takes varies from person to person and it is important to realise that some unmet needs may not become an issue until much later on.

7.2 Rationale for follow-up

From an oncological perspective, surveillance is important as early detection of recurrence may increase the likelihood of curative treatment. Some studies suggest local recurrence does not significantly reduce long-term survival if successfully treated [147, 303]. However, a recent multi-centre study reported an increased risk of recurrence following glansectomy in men with more aggressive disease (T3 and/or high grade), which in turn resulted in poorer OS and CSS [145]. Disease that has spread to the inguinal LNs greatly reduces the rate of long-term CSS. Follow-up is also important for survivorship, allowing for the detection and management of the physical and psychological impact of treatments. The use of Patient Reported Outcome Measures (PROMS)

related to body image (Male Genital Self-Image Scale MGSIS-5) and lymphoedema (Groin and Lower Limb lymphoedema questionnaire G3L-20) have been proposed as tools to help patients and their healthcare team raise and discuss embarrassing topics during consultations [304].

Local or regional nodal recurrences usually occur within two to three years of primary treatment [147, 305, 306]. A recent study of 509 patients reported 52.3% of local recurrences occurred within two years and 79.5% within three years [306]. Fewer than 5% of regional or distant recurrences occur after two years, with the majority occurring within the first year after treatment [305, 306]. After five years, all recurrences were either local or new primary lesions [147]. This supports an intensive follow-up regimen during the first two years, with a less intensive follow-up later for a total of at least five years. Follow-up after five years may be omitted in motivated patients who will undertake regular self-examination reliably [147].

7.2.1 ***When and how to follow-up***

After local treatment with negative inguinal nodes, follow-up should include physical examination of the penis and 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 (imaging of thorax, abdomen and pelvis) should be performed at 3-monthly intervals for the first two years. Following this, the frequency is usually reduced to 6-monthly for a total of 5 years of follow-up. However, one study of 224 node-positive patients reported only two recurrences in years 3–5 of follow-up, and both of these were pN3 patients [305]. Although rare, late local recurrence may occur. Therefore, regular follow-up can be stopped after 5 years, provided the patient understands the need to report any local changes immediately [98]. In patients unlikely to self-examine, long-term follow-up may be necessary (Table 7.1).

7.2.2 ***Recurrence of the primary tumour***

Local recurrence is more likely with all types of local organ-sparing treatment. Until recently it was not believed to influence the CSS rate, although one study recently challenged this showing a reduction in OS and CSS following local recurrence after glansectomy [145]. Large series of glansectomies have reported local recurrence rates around 10% [145, 307], although others have reported recurrence in up to 27% of patients treated with penis-preserving modalities, usually occurring within the first two years [146]. After partial penectomy, the risk of local recurrence is about 4–5% [146, 147, 303]. 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.

7.2.3 ***Regional recurrence***

Most regional recurrences occur during the first two years after treatment, irrespective of whether surveillance or invasive nodal staging were used. Although unlikely, regional recurrence can occur later than two years after treatment. It is therefore advisable to continue follow up in these patients [98]. The highest rate of regional recurrence (9%) occurs in patients managed by surveillance, while the lowest is in patients who have undergone invasive nodal staging by modified ILND or DSNB and whose LNs were negative (2.3%). The use of US and FNAC in suspicious cases has improved the early detection rate of regional recurrence [106, 107, 308]. Patients who have had surgery for LN metastases without adjuvant treatment have an increased risk of regional recurrence of 19% [147]. Regional recurrence requires timely treatment by rILND with (neo)adjuvant chemotherapy/chemo-radiotherapy.

Table 7.1: Follow-up regime for penile cancer

	Interval of surveillance		**Examinations and investigations**	**Minimum duration of follow-up**
	Years 1–2	Years 3–5		
Recommendations for follow-up of the primary tumour				
Penile-preserving treatment	3-monthly	6-monthly	Regular physician or self-examination. Repeat biopsy after topical or laser treatment for PeIN (optional).	5 years
Amputation	3-monthly	Annually	Regular physician or self-examination.	5 years
Recommendations for follow-up of the inguinal lymph nodes				
Surveillance	3-monthly	6-monthly	Regular physician or self-examination. US ± FNAC optional.	5 years
pN0	3-monthly	Annually	Regular physician or self-examination. US ± FNAC optional.	5 years

pN+	3-monthly	6-monthly	Regular physician or self-examination. US ± FNAC, CT chest/abdomen/pelvis or ^{18}FDG-PET/CT optional.	5 years

CT = computed tomography; ^{18}FDG = ^{18}F-fluoro-2-deoxy-D-glucose; FNAC = fine needle aspiration cytology; PET = positron emission tomography; US = ultrasound.

7.3 Patient support services

Surveillance is not just about assessing for recurrent disease and men may require more frequent appointments than suggested above, with different members of the multi-disciplinary team to deliver patient support services and address QoL challenges. In fact, the latter starts at the first pre-operative consultation, where a needs assessment can identify areas that will be individually more challenging for that patient, be it physical, psychological, emotional, social or financial. Many men with penile cancer reflect that whilst the knowledge of potential functional and psychological impacts of treatment would not have stopped them proceeding with it, they wish they had a better understanding before embarking on the surgery. Pre-habilitation programmes can also help with this. Recently a qualitative study highlighted that men with penile cancer would appreciate more focus on the following themes: "early signs and seeking help", "disclosure of a personal cancer" and "urological (dys)function" [309].

Unfortunately, not all men survive penile cancer and some present with, or recur with, advanced disease, some with extremely challenging symptoms to manage, including pain, odour and discharge. In addition to medical treatments outlined in other parts of these guidelines, early involvement of palliative care services for symptom control can make a huge difference to these patients.

7.3.1 Psychological support

Access to psychological support, counselling and psychosexual therapy are critical components of a holistic and multi-disciplinary survivorship service. Men will often think "why me?" and need help to process their thoughts and try to adjust to their changing situation. Areas for discussion might include identity and self-esteem (lifestyle and role adjustments), being a perceived burden, illness beliefs and perceptions, levels of social support, relationship quality and intimacy, body and self-image and concerns around mortality. Despite these significant psychological challenges, the rate of suicide, based on the SEER database (1973–2013) is amongst the lowest of all urological malignancies; 13 out of 6,155 men [310].

7.3.2 Quality of life

There is very little data on QoL after treatment for penile cancer. In particular, there is heterogeneity of the psychometric tools used to assess QoL outcomes and further research is needed to develop disease-specific PROMS for penile cancer. Some validated questionnaires have been used but none of them were validated in men with penile cancer. Tools used include LYMQOL (lymphoedema) [311], IIEF (erectile dysfunction) [312], SF-36 [313], European Organization for Research and Treatment of Cancer [EORTC] QLQ-C30 [314], Quality of Life Questionnaire-Penile Cancer-Rostock (HRO-PE29) [315], Hospital Anxiety and Depression Scale [316], EQ-5D (Euro QoL tool), Bigelow's questionnaire [317], Male Genital Self-Image Scale MGSIS-5 and Groin and Lower Limb lymphoedema questionnaire G3L-20 [318].

Not surprisingly, published studies and discussions with patient groups demonstrate that penile cancer and its treatments have a significant impact on overall QoL, both physical and psychological. However, there is discrepancy in the literature as to whether partial penectomy impacts QoL more than penile-preserving surgical techniques, as discussed below. Erectile dysfunction, reduced frequency of sexual intercourse and reduced satisfaction with intercourse are reported in some studies [319, 320]. Urinary spraying [321] is another potential significant consequence of penile cancer surgery. Significant anxiety (31%) and depression (6%) has also been reported [322].

A German study reported on 76 patients following primary penile surgery. They reported a global QoL score well below the national average for age-standardised German patients, with voiding, sexuality, body image, lymphoedema all reported as areas of concern [315].

A Dutch study, where 90 patients returned their questionnaires (a return rate of 62%) orgasm, appearance concerns, life interference and urinary function were all significantly poorer following partial penectomy compared with a penile-preserving approach. In the same study, LND had a significant impact on life interference. Interestingly, when compared to an age and gender matched normative sample from the general population the patients reported better outcomes for the SF-36 physical domain and bodily pain sub scale [321].

A recent SR [3] reported on post-treatment QoL from 10 studies involving 346 men [157, 176, 315, 321, 323-328]. Two studies evaluated QoL as the primary endpoint and compared the outcomes among various treatment modalities [323, 327]. One of these studies used EORTC QLQ C-30 and reported on the QoL of men after penile cancer management with different treatment modalities. They observed that the treatment itself was not related to overall wellbeing or to social contact and activity. However, half of the individuals had psychological symptoms at follow-up [327]. In contrast, a retrospective study of men who underwent penile-preserving surgery reported a significant impact of surgery in every domain of EORTC QLQ-C30 questionnaire [315].

Another study used Bigelow's questionnaire and compared the post-operative QoL score to that at two weeks before surgery [328]. It reported that the scores relating to unpleasant feeling, sexual pleasure and familial/ partner relations improved significantly ($p < 0.01$) whereas the domains relating to friend relationships and professional quality were unchanged.

Two non-randomised comparative studies used EORTC QLQ-C30 to assess QoL after penile preserving surgery or amputative surgery [323, 324]. The first trial on 51 men reported a statistically significant negative correlation between aggressiveness of surgery and global health status and physical functioning [323]. Whereas the other reported no significant differences between penile-preserving surgery or partial penectomy in functional scale, symptom scale and in the global health status [324]. A comparison between glans resurfacing, glansectomy and partial penectomy using the EQ-5D tool showed no difference between groups with comparable health status scores of 82.5, 85.0 and 87.5 respectively [157].

Another non-randomised comparative study also compared penile-preserving surgery to partial penectomy and reported no difference in QoL using the SF-36 scores [321]. Those who underwent amputative surgery had significantly more appearance concerns ($p = 0.008$) and they reported more life interference ($p = 0.032$) depending on the degree of disfigurement caused by the procedure.

*7.3.3 **Urinary function***

Urinary function is an important topic to discuss with men before penile cancer treatment. Some will already be experiencing difficulty voiding due to their tumour causing urethral obstruction and many report they sit down to pass urine due to the spraying caused by the tumour. As a result, some report improved function following surgery, often in terms of flow but spraying and needing to sit down to void or use a funnel/bottle can be debilitating for many men.

Urinary function has been objectively assessed in only a few studies. Two case series reported improvement in post-operative urinary function and high satisfaction after penile surgery [326, 329]. Two non-randomised comparative studies reported no difference in urination between penile-preserving surgery or amputation. One demonstrated similar maximum flow rates following surgery (19.5 mL/s vs. 20.8 mL/s) [324] the other reported that urinary function was comparable across the study groups (glans resurfacing, glansectomy and partial penectomy) using the ICIQ-MLUTS score [157]. However, a different study found that urine spraying is more common after partial penectomy as compared to penile-preserving surgery (83% vs. 43%) [321]. Two case series reported no significant changes in urinary function following brachytherapy [166, 176]. A single trial on Moh's micrographic surgery, reported no post-treatment change (66% response rate) [330].

*7.3.4 **Sexual function***

Sexual and erectile function after penile cancer varies between studies and between treatments. Generally, penile-preserving surgery preserves erectile function, although glans sensation and orgasm can be affected. Overall, partial penectomy is associated with poorer sexual outcomes.

A recent SR [3] reported on the sexual and erectile function from 27 studies that involve 991 men. The 5- or 15-question International Index of Erectile Function (IIEF) scores were used by most studies. Other tools used were the Erectile Dysfunction Inventory of treatment satisfaction score (EDITS), the index of male genitalia image (IM-GI), the Life Satisfaction of sexual life, the SELF-Esteem and Relationship (SEAR) or a combination of tools to assess overall sexual function [176, 324, 325, 327, 331]. It is important to acknowledge that only a few studies assessed baseline function and are therefore able to report the difference between pre- and post-treatment. Most studies reported only the post-treatment scores or the mean difference for retrospectively completed pre-treatment scores.

Three non-randomised comparative studies and one case series assessed the impact of penile-preserving surgery vs. amputation on sexual function of 202 men [321, 324, 327, 332]. Two studies that used the 15-question IIEF questionnaire reported significant post-treatment changes in the orgasmic function domain in favour of penile-preserving surgery ($p = 0.033$ and $p = 0.033$) while the other domains remain comparable between the treatment arms [321, 324]. However, in other studies using the 5-question IIEF score, no difference was identified between treatments [157, 332]. An older study that compared the impact of penile-preserving surgery, amputative surgery and radiotherapy on sexual function reported that those treated with amputation had worst sexual outcome [327]. Three trials retrospectively compared penile-preserving surgery techniques using IIEF questionnaire [326, 333, 334]. Wide local excision was superior to glansectomy in all IIEF domains [333]. The impact of primary closure versus preputial flap reconstruction after glans-preserving surgery was similar as seen by IIEF results at 6 months or by rigid-scan parameters [334]. Partial glansectomy was not superior to total glansectomy [326].

Cohort studies have reported similar findings on sexual function. Five studies on patients who underwent penile-preserving surgery and reconstruction reported that 85–100% of men were able to achieve erection and maintain their sexual function [158, 335-338]. However, all patients reported reduced glans sensitivity. Following glans resurfacing for penile cancer (n = 21) or lichen sclerosis (n = 16) one study reported no significant change in urinary or sexual function (using IPPS and IIEF questionnaires) with glans sensitivity preserved in 89.2% of men [339].

Four studies on 167 men who have had partial penectomy reported significant changes in 15-question IIEF score with negative impact in every domain [319, 329, 331, 340]. A single trial reported that 61.7% of men after partial penectomy report erectile dysfunction [340]. However, a study from Brazil, assessing 14 patients following partial penectomy, found that for 64% overall sexual function was normal or slightly decreased and frequency of sexual intercourse was unchanged or slightly decreased [320].

The sexual function after brachytherapy has been assessed in five cohort studies [162, 166, 176, 341, 342]. Among men who were sexually active before treatment, 58.8–70.0% remain sexually active after treatment [162, 176]. Potency was maintained in 81.5–100% of men [162, 166, 176, 341, 342]. Altered glans sensitivity is reported in 52.6% [162].

Three studies assessed sexual function after laser treatment [155, 325, 343] and 46–56.5% of men report an impact of treatment on their sexual life [325, 343]. A single trial on 46 men found that 72% reported no change in erectile function, 22% reported decreased erectile function and 6% reported improvement [155].

One trial on patients who underwent Moh's micrographic surgery reported no change in sexual function after treatment (57.5% response rate) [330].

7.3.5 ***Lymphoedema***

Lymphoedema significantly impacted functional domains in one study of patients 25 months following penile cancer nodal surgical treatment with inguinal and PLND having a much higher impact than ILND alone. Patients who had inguinal and PLND also had a much poorer mood score (38% vs. 0%) [344]. Due to the significant morbidity associated with ILND, many patients are not offered the operation or choose not to have it. An analysis of the US SEER database reported that only 233 out of 943 nonmetastatic penile cancer patients (24.7%) had ILND between 1998 and 2015 [223]. This did not change over time. A similar proportion of men, 606 out of 2224 (27.2%) underwent the surgery between 2004 and 2014 as recorded by the National Cancer Database [345].

Men should be assessed for genital and lower limb lymphoedema at each outpatient clinic appointment, advised about good skin care, compression, exercise, massage, and elevation when resting as the mainstay of treatment. Following nodal surgery, ideally, they would be referred to specialist lymphoedema services for assessment and management before any significant lymphoedema occurs.

Specialist lymphoedema services offer a range of made-to-measure compression garments or multi-layer lymphoedema bandaging for lower limb and genital lymphoedema. The latter not only compress the scrotal lymphoedema but also aim to lift it to aid drainage. For lower limb compression adjustable Velcro garments also exist. Good skin care is critical to prevent infection that can damage remaining lymphatic channels. Prophylactic antibiotics should be used following any episode of cellulitis, with penicillin V, erythromycin or clindamycin recommended, except in genital lymphoedema where prophylactic trimethoprim can be used [346].

Manual lymphatic drainage in the form of specialised massage techniques also helps to alleviate lymphoedema and encourages drainage. Following penile cancer treatments this is commonly used for stubborn mons and lower abdominal swelling and thickening of the scrotum and penile shaft.

Whilst regular exercise may temporarily increase lymphoedema due to the effect of gravity, it has an overall beneficial effect on lymphoedema by reducing abdominal fat (fat drains via lymphatic channels too) and using natural muscle pumps and changes in thoracic pressure to help lymphatic drainage. Strength training and stretching exercises to promote flexibility are also important.

Debulking surgery with scrotal reduction and penile shaft skin grafting can significantly improve issues related to significant genital lymphoedema. There is limited evidence for the benefit of other surgical interventions such as limb liposuction followed by compression and lymphatico-venous anastomosis in penile cancer although some evidence does exist for extremity lymphoedema due to various causes [347].

7.4 Centralisation of penile cancer services

Current large volume centres offer specialist nursing support, psychological support and specialised lymphoedema services to their patients. However, even in centralised healthcare systems, such as the UK, services vary and are not always available.

Centralisation of penile cancer services has a number of advantages in addition to delivering these important supportive services to patients (Table 7.2) [348]. These include provision of an environment where multi-disciplinary discussion of cases can occur along with specialist pathological review, and delivery of high volume penile-preserving and nodal surgery which can lead to innovation, such as closer surgical margins [151], more accurate DSNB and minimally-invasive surgery. In the UK, around 80% of penile cancers are treated with penile-preserving surgery. Centralisation can also reduce system delays [349] and result in better adherence to guidelines. In addition, patients should be able to access a larger team of specialists, including psychological and lymphoedema survivorship services. Centralisation of penile cancer services also creates opportunities for research and running clinical trials with a larger number of patients in a rare disease.

Disadvantages of centralisation include de-skilling of medical teams not involved with regularly looking after penile cancer and making patients travel long distances for treatment. This can be a significant financial burden, especially as many are in a lower socio-economic group. However, the recent increase in virtual healthcare and video consultation may reduce this burden, as does the provision of outreach clinics and services. In addition, educational sessions within cancer networks, can help keep local teams up-to-date, enabling them to help support the patient when back at home (Table 7.2).

In one hospital in the UK, 5-year CSS rates were observed to improve by up to 12% to 85% following centralisation, which is likely to be due to several factors, including the impact of early and complete pathological LN staging, regular multi-disciplinary patient reviews and use of adjuvant chemotherapy and chemo-radiotherapy in most patients where indicated [350].

Table 7.2: Advantages and disadvantages of centralisation

Advantages	Disadvantages
Multi-disciplinary team and holistic approach to penile cancer care	De-skilling of urologists and their teams
Opportunities for research, clinical trials and innovation	Distance patients need to travel
Improved survival	Financial burden of travel
High rates of penile-preserving surgery	Lack of local support for patients
High rates of surgical nodal staging	
Specialist lymphoedema services	
Specialist uro-radiology/nuclear medicine	
Specialist pathology reporting/review	
Psychological support	
Adherence to guidelines	
Clear referral pathway/reduced system delays	

7.5 Summary of evidence and guidelines for follow-up and quality of life

Summary of evidence	LE
Follow-up surveillance is important as early detection of recurrence may increase the likelihood of curative treatment.	3
Local or regional nodal recurrences usually occur within two years of primary treatment.	3
Penile cancer has a significant impact on QoL in many ways and there remain many unmet needs to address.	4
There is very little data on QoL after treatment for penile cancer. In particular, there is heterogeneity of the psychometric tools used to assess QoL outcomes and further research is needed to develop disease-specific PROMS for penile cancer.	3
Generally, penile-preserving surgery preserves erectile function, although glans sensation and orgasm can be affected. Overall, partial penectomy is associated with poorer sexual outcomes.	2b
Access to psychological support, counselling and psychosexual therapy are critical components of a holistic and multi-disciplinary patient support service.	4
Ideally, following nodal surgery, patients would be referred to specialist lymphoedema services for assessment and management before any significant lymphoedema occurs.	4
In one UK specialist penile cancer centre (referral population approximately 11 million), 5-year CSS rates were observed to improve by up to 12-85% following centralisation.	3

Recommendations	Strength rating
Deliver penile cancer care as part of an extended multi-disciplinary team comprising of urologists specialising in penile cancer, specialist nurses, pathologists, uro-radiologists, nuclear medicine specialists, medical and radiation oncologists, lymphoedema therapists, psychologists, counsellors, palliative care teams for early symptom control, reconstructive surgeons, vascular surgeons, sex therapists.	Strong
Follow-up men after penile cancer treatment, initially 3-monthly for two years then less frequently to assess for recurrent disease and to offer patient support services through the extended multi-disciplinary team. At discharge, recommend self-examination with easy access back to the clinic as local recurrence can occur late.	Strong
Discuss the psychological impact of penile cancer and its treatments with the patient and offer psychological support and counselling services.	Strong
Discuss the negative impact of treatments for the primary tumour on penile appearance, sensation, urinary and sexual function so that the patient is better prepared for the challenges he may face.	Strong
Discuss the potential impact of lymphoedema as a consequence of inguinal and pelvic lymph node treatment with the patient and assess patients for it at follow-up and refer to lymphoedema therapists early.	Strong

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9. CONFLICT OF INTEREST

All members of the EAU-ASCO Penile Cancer Guidelines working group have provided disclosure statements of all relationships that they have that might be perceived as a potential source of a conflict of interest. This information is publicly accessible through the European Association of Urology website: http://uroweb.org/guideline/penile-cancer/.

This guidelines document was developed with the financial support of the European Association of Urology. No external sources of funding and support have been involved. The EAU is a non-profit organisation and funding is limited to administrative assistance and travel and meeting expenses. No honoraria or other reimbursements have been provided.

10. CITATION INFORMATION

The format in which to cite the EAU Guidelines will vary depending on the style guide of the journal in which the citation appears. Accordingly, the number of authors or whether, for instance, to include the publisher, location, or an ISBN number may vary.

The compilation of the complete Guidelines should be referenced as:
EAU-ASCO Penile Cancer Guidelines. Edn. presented at the EAU Annual Congress Paris 2024. ISBN 978-94-92671-23-3.

If a publisher and/or location is required, include:
EAU Guidelines Office, Arnhem, The Netherlands. http://uroweb.org/guidelines/compilations-of-all-guidelines/

References to individual guidelines should be structured in the following way:
Contributors' names. Title of resource. Publication type. ISBN. Publisher and publisher location, year.

EAU Guidelines on

Urolithiasis

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1. INTRODUCTION

1.1 Aims and scope

The European Association of Urology (EAU) Urolithiasis Guidelines Panel has prepared these guidelines to help urologists assess evidence-based management of stones/calculi in the urinary tract and incorporate recommendations into clinical practice. This document covers most aspects of the disease, which is still a cause of significant morbidity despite technological and scientific advances. The Panel is aware of the geographical variations in healthcare provision. In addition, information on the management of bladder stones is now also included in these guidelines.

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

1.2 Panel composition

The EAU Urolithiasis Guidelines Panel consists of an international group of clinicians with expertise in this area. All experts involved in the production of this document have submitted potential conflict of interest 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. This is an abridged version, which may require consultation together with the full-text versions. Several scientific publications are available [1-3]. All documents are accessible through the EAU website Uroweb: http://uroweb.org/guideline/urolithiasis/.

1.4 Publication history and summary of changes

*1.4.1 **Publication history***

The EAU Guidelines on Urolithiasis 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. This 2024 Urolithiasis Guidelines present a limited update of the 2023 publication.

*1.4.2 **Summary of changes***

The 2024 Urolithiasis Guidelines have undergone a major revision and restructuring of text, as well as a review of all recommendations.

2. METHODS

2.1 Data identification

Recommendation within the Guidelines are developed by the panels to prioritise clinically important care decisions. The strength of each recommendation is determined by the balance between desirable and undesirable consequences of alternative management strategies, the quality of the evidence (including certainty of estimates), and the nature and variability of patient values and preferences. This decision process, which can be reviewed in the strength rating forms which accompany each guideline statement, addresses a number of key elements:

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

Strong recommendations typically indicate a high degree of evidence quality and / or a favourable balance of benefit to harm and patient preference. Weak recommendations typically indicate availability of lower quality evidence, and/or equivocal balance between benefit and harm, and uncertainty or variability of patient preference [5].

Additional information can be found in the general Methodology section of this print, and online at the EAU website: https://uroweb.org/guidelines/urolithiasis/ publications-appendices. A list of associations endorsing the EAU Guidelines can also be viewed online at the above address.

2.2 Review

The 2015 Urolithiasis Guidelines were subjected to peer review prior to publication. Chapter 6, detailing the treatment and follow-up of bladder stones was peer-reviewed in 2019.

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% [6]. In countries with a high standard of life such as Sweden, Canada or the USA, renal stone prevalence is notably high (> 10%). For some areas, an increase of more than 37% over the last 20 years has been reported [7-9]. There is emerging evidence linking nephrolithiasis to the risk of chronic kidney disease (CKD) [10].

Stones can be stratified into those caused by: infections, non-infectious causes, genetic defects [11, 12]; or adverse drug effects (drug stones) (Table 3.1). See also section 3.2.

Table 3.1: Stones classified by aetiology

Non-infection stones		
• Calcium oxalate	• Calcium phosphate	• Uric acid • Ammonium urate*
Infection stones		
• Magnesium ammonium phosphate	• Highly carbonated apatite	• Ammonium urate
Genetic causes		
• Cystine	• Xanthine	• 2,8-Dihydroxyadenine
Drug stones		

**In children in developing countries; in patients with anorexia or laxative-abuse.*

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 3.2 lists the most clinically relevant substances and their mineral components.

Table 3.2: Stone composition

Chemical name	Mineral name [13]	Chemical formula
Calcium oxalate monohydrate	Whewellite	$CaC_2O_4.H_2O$
Calcium oxalate dihydrate	Weddelite	$CaC_2O_4.2H_2O$
Basic calcium phosphate	Apatite	$Ca_{10}(PO_4)_6.(OH)_2$
Calcium hydroxyl phosphate	Carbonate apatite	$Ca_5(PO_4)_3(OH)$
b-tricalcium phosphate	Whitlockite	$Ca_3(PO_4)_2$
Carbonate apatite phosphate	Dahllite	$Ca_5(PO_4)_3OH$
Calcium hydrogen phosphate dihydrate	Brushite	$CaHPO_4.2H_2O$
Calcium carbonate	Aragonite	$CaCO_3$
Octacalcium phosphate	-	$Ca_8H_2(PO_4)_6.5H_2O$
Uric acid	Uricite	$C_5H4N_4O_3$

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 hexahydrate	Struvite	$MgNH_4PO_4.6H_2O$
Magnesium acid phosphate trihydrate	Newberyite	
Magnesium ammonium phosphate monohydrate	Dittmarite	
Cystine	-	
Xanthine	-	-
2,8-Dihydroxyadenine	-	-
Proteins	-	-
Cholesterol	-	-
Calcite	-	-
Potassium urate	-	-
Trimagnesium phosphate	-	-
Melamine	-	-
Matrix	-	-
Drug stones	Active compounds crystallising in urine	-
Foreign body calculi	-	-

*3.1.3 **Risk groups for stone formation***

Determination of the risk for stone formation is imperative for pharmacological treatment. Previous stone history (recurrence, regrowth, stone surgeries) is a fundamental element in determining risk for stone formation. About 50% of recurrent stone formers have just one-lifetime recurrence [9, 14]. A review of first-time stone formers calculated a recurrence rate of 26% in five years' time [15]. Highly recurrent disease is observed in slightly more than 10% of patients. Stone type and disease severity determine low- or high-risk stone formers (Table 3.3) [16-32].

However, the risk status of stone formers should be determined in a holistic way taking into consideration not only the probability of stone recurrence or regrowth, but also the risk of chronic kidney disease (CKD), end-stage kidney disease (ESKD), and metabolic bone disorder (MBD) [33, 34]. A comprehensive evaluation of stone risk in patients should also include the risk of developing CKD, ESKD, and MBD (Tables 3.4, 3.5, and 3.6) [33]. Urolithiasis can compromise renal function because of the renal stone (obstruction, infection), renal tissue damage due to the primary condition causing stone formation (some genetic diseases, nephrocalcinosis, enteric hyperoxaluria, etc.), or urological treatments for the condition [33]. Certain risk factors have been shown to be associated with such a risk in stone formers, as shown below.

Table 3.3: High-risk stone formers [16-32]

General factors
Early onset of urolithiasis (especially children and teenagers)
Familial stone formation
Recurrent stone formers
Short time since last stone episode
Brushite-containing stones ($CaHPO_4.2H_2O$)
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 crucial importance to avoid acute renal failure)
Chronic Kidney Disease (CKD)

Diseases associated with stone formation
Hyperparathyroidism
Metabolic syndrome
Mineral Bone Disorder (MBD)
Nephrocalcinosis
Polycystic kidney disease (PKD)
Gastrointestinal diseases (i.e., enteric hyperoxaluria due to jejuno-ileal bypass, intestinal resection, Crohn's disease, malabsorptive conditions, urinary diversion, exocrine pancreatic insufficiency, and bariatric surgery).
Increased levels of vitamin D
Sarcoidosis
Spinal cord injury, neurogenic bladder
Genetically determined stone formation
Cystinuria (type A, B and AB)
Primary hyperoxaluria (PH)
Renal tubular acidosis (RTA) type I
2,8-Dihydroxyadeninuria
Xanthinuria
Lesch-Nyhan syndrome
Cystic fibrosis
Drug-induced stone formation (see Table 4.11)
Anatomical abnormalities associated with stone formation
Medullary sponge kidney (tubular ectasia)
Ureteropelvic junction (UPJ) obstruction
Calyceal diverticulum, calyceal cyst
Ureteral stricture
Vesico-uretero-renal reflux
Horseshoe kidney
Ureterocele
Environmental and professional factors
High ambient temperatures
Chronic lead and cadmium exposure

Table 3.4 Risk factors for CKD and ESKD in stone formerss

Risk factors for CKD/ESKD in stone formers
Female gender
Overweight
Frequent UTI
Struvite stones
Acquired single kidney
Neurogenic bladder
Previous obstructive nephropathy
Ileal conduit

Furthermore, some specific kinds of urolithiasis also carry a particular risk of developing CKD/ESKD as shown below.

Table 3.5 Risk factors for CKD and renal stones

Risk of chronic kidney disease and renal stones
• Possible risk of CKD
■ Xanthine stones
■ Indinavir stones
■ Distal renal tubular acidosis (incomplete)
■ Primary hyperparathyroidism
■ Eating disorders and laxative abuse
■ Medullary sponge kidney
• Moderate risk of CKD
■ Brushite stones
■ 2,8-Dihydroxyadenine stones
■ Sarcoidosis
■ Pyelo-ureteral or ureteral strictures
• High risk of CKD
■ Cystine stones
■ Struvite stones
■ Stones in a single kidney
■ Distal renal tubular acidosis (complete)
■ Secondary hyperoxaluria (bariatric surgery, inflammatory bowel disease, bowel resection and malabsorptive syndromes)
■ Other forms of nephrocalcinosis (often associated with genetic conditions with hypercalciuria)
■ Anatomical abnormalities of the kidney and urinary tract (for example, horseshoe kidney, ureterocele and vesicoureteral reflux)
■ Neurological bladder
• Very high risk of CKD
■ Primary hyperoxaluria
■ Autosomal dominant polycystic kidney

Table 3.6 Risk factors for metabolic bone disease and calcium renal stones

Risk of metabolic bone disease and calcium renal stones
• Distal renal tubular acidosis (complete or incomplete)
• Medullary sponge kidney
• Primary hyperparathyroidism
• Malabsorptive syndromes
• Fasting hypercalciuria
• Genetic disorders

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 [2, 9, 32].

*3.2.1 **Stone size***

Stone size can be reported in a single, two or three dimensions. Currently, the guidelines still use the linear measurement of cumulative stone diameter to stratify stones in < 5 mm, 5-10 mm, 10-20 mm, and > 20 mm for use in the treatment algorithm.

*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.

3.2.3 X-ray characteristics

Stones can be classified according to plain X-ray appearance [kidney-ureter-bladder (KUB) radiography] (Table 3.7), which varies according to mineral composition [35]. 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 3.3) [35, 36].

Table 3.7: X-ray characteristics

Radiopaque	Poor radiopacity	Radiolucent
Calcium oxalate dihydrate	Magnesium ammonium phosphate	Uric acid
Calcium oxalate monohydrate	Cystine	Ammonium urate
Calcium phosphate		Xanthine
		2,8-Dihydroxyadenine
		Drug-stones (Section 4.11)

3.3 Diagnostic evaluation

3.3.1 Diagnostic imaging

The most appropriate imaging modality will be determined by the clinical situation, which will differ depending on if a ureteral or a renal stone is suspected.

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 [37]. Immediate evaluation is indicated in patients with solitary kidney, fever or when there is doubt regarding a diagnosis of renal colic. 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 calyces, pelvis, and pyeloureteric and vesico-ureteral junctions (US with filled bladder), as well as in patients with upper urinary tract (UUT) dilatation. Ultrasound has a sensitivity of 45% and specificity of 94% for ureteral stones and a sensitivity of 45% and specificity of 88% for renal stones [38, 39].

The sensitivity and specificity of KUB is 44-77% [40]. Kidney-ureter-bladder radiography [41] is helpful in differentiating between radiolucent and radiopaque stones and could be used for comparison during follow-up.

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 CT can determine stone location, burden, and density. When stones are absent, the cause of abdominal pain should be identified. In evaluating patients with suspected acute urolithiasis, NCCT is significantly more accurate than IVU or US [42, 43].

Non-contrast-enhanced CT can detect uric acid and xanthine stones, which are radiolucent on plain films, but not indinavir stones [44]. Non-contrast-enhanced CT can determine stone density, the inner structure of the stone, skin-to-stone distance, and surrounding anatomy; all of which affect the selection of treatment modality [45]. The advantage of non-contrast imaging must be balanced against the loss of information on renal function and urinary collecting system anatomy, as well as higher radiation dose [46-49].

Radiation risk can be reduced by low-dose CT, which may, however, be difficult to introduce in standard clinical practice [50-53]. In patients with a body mass index (BMI) < 30, low-dose CT has been shown to have a sensitivity of 86% for detecting ureteral stones < 3 mm and 100% for calculi > 3 mm [54]. A meta-analysis (MA) of prospective studies [55] has shown that low-dose CT diagnosed urolithiasis with a pooled sensitivity of 93.1% (95% CI: 91.5-94.4), and a specificity of 96.6% (95% CI: 95.1-97.7%). Dual-energy CT can differentiate uric acid containing stones from calcium-containing stones [36].

Summary of evidence	LE
Non-contrast-enhanced CT is used to confirm stone diagnosis in patients with acute flank pain, as it is superior to IVU.	1a
Computed tomography imaging enables 3D reconstruction of the collecting system, as well as measurement of stone density and skin-to-stone distance.	2a
Consider a contrast study if stone removal is planned and the anatomy of the renal collecting system needs to be assessed.	3

Recommendations	Strength rating
Immediate imaging is indicated with fever or solitary kidney, and when diagnosis is doubtful.	Strong
Use non-contrast-enhanced computed tomography to confirm stone diagnosis in patients with acute flank pain following initial ultrasound assessment.	Strong

*3.3.2 **Diagnostics - metabolism-related***

Besides imaging, each emergency patient with urolithiasis needs a succinct biochemical work-up of urine and blood test. At this point, no distinction is made between high- and low-risk patients for stone formation.

3.3.2.1 Basic laboratory analysis - non-emergency urolithiasis patients

Biochemical work-up is similar for all stone patients (see 3.3.2.3). However, if no intervention is planned, examination of sodium, potassium, C-reactive protein (CRP), and blood coagulation time can be omitted. Only patients at high risk for stone recurrence should undergo a more specific analytical programme [17]. Stone-specific metabolic evaluation is described in Chapter 4.

The easiest method for diagnosing stones is by analysis of a passed stone using a validated method as listed in section 3.3.2.3. Once the mineral composition is known, a potential metabolic disorder can be identified.

3.3.2.2 Analysis of stone composition

Stone analysis should be performed on 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 [56, 57].

Patients should be instructed to filter their urine to retrieve a concrement for analysis. Stone passage and restoration of baseline renal function should be confirmed.

The preferred analytical procedures are infrared spectroscopy (IRS) or X-ray diffraction (XRD) [58, 59]. Equivalent results can be obtained by polarisation microscopy. Chemical analysis (wet chemistry) is generally deemed to be obsolete [58, 60].

3.3.2.3 Recommendations for laboratory examinations and stone analysis [17, 23, 61-63]

Recommendations	Strength rating
Urine	
Dipstick test of spot urine sample: • red cells; • white cells; • nitrites; • approximate urine pH; • urine microscopy and/or culture.	Weak
Blood	
Serum blood sample: • creatinine; • uric acid; • (ionised) calcium; • sodium; • potassium; • blood cell count; • C-reactive protein.	Strong
Perform a coagulation test (partial thromboplastin time and international normalised ratio) if intervention is likely or planned.	Strong
Perform stone analysis in first-time formers using a valid procedure (X-ray diffraction or infrared spectroscopy).	Strong

Repeat stone analysis in patients presenting with: • recurrent stones despite drug therapy; • early recurrence after complete stone clearance; • late recurrence after a long stone-free period because stone composition may change.	Strong

*3.3.3 **Diagnosis in special groups and conditions***

3.3.3.1 Diagnostic imaging during pregnancy

In pregnant women, radiation exposure may cause non-stochastic (teratogenesis) or stochastic (carcinogenesis, mutagenesis) effects. Teratogenic effects are cumulative with increasing doses and require a threshold dose (< 50 mGy are considered as safe) and depend on the gestation age (minimum risk prior to the 8th week and after the 23rd week). Carcinogenesis (dose even < 10 mGy present a risk) and mutagenesis (500-1000 mGy doses are required, far in excess of the doses in common radiographic studies) get worse with increasing dose but they do not require a dose threshold and are not dependent on the gestational age [64].

There is no imaging modality that should be routinely repeated in pregnant women. Scientific societies and organizations agree on the safety of the diagnostic evaluation when the US [65], X-ray imaging [66, 67], and MRI [68] are used as and when indicated [69-76]. A radiographic procedure should not be withheld from a pregnant woman if the procedure is clearly indicated and doing so will affect her medical care.

It is generally recommended that an investigation resulting in an absorbed dose to the foetus of greater than 0.5 mGy requires justification.

Ultrasound (when necessary, using changes in the 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 [72-74].

Magnetic resonance imaging can be used, as a second-line option [70], to define the level of urinary tract obstruction, and to visualise stones as a filling defect [77]. The use of gadolinium is not routinely recommended in pregnancy to avoid toxic effects on the embryo [72].

For the detection of urolithiasis during pregnancy, low-dose CT is associated with a higher positive predictive value (95.8%), compared to MRI (80%) and US (77%). As per White *et al.*, low-dose CT offers improved diagnostic accuracy that can avoid negative interventions such as ureteroscopy [78]. Although low-dose CT protocols reduce radiation exposure, judicious use is currently recommended in pregnant women as a last-line option [72].

Summary of evidence	**LE**
Only low-level data exist for imaging in pregnant women supporting US and MRI.	3

Recommendations	**Strength rating**
Use ultrasound as the preferred method of imaging in pregnant women.	Strong
Use magnetic resonance imaging as a second-line imaging modality in pregnant women.	Strong
Use low-dose computed tomography as a last-line option in pregnant women.	Strong

3.3.3.2 Diagnostic imaging in children

Children with urinary stones have a high risk of recurrence; therefore, standard diagnostic procedures for high-risk patients apply, including a valid stone analysis (Section 3.1.3 and Chapter 4). The most common nonmetabolic disorders facilitating stone formation are vesicoureteral reflux (VUR), UPJ obstruction, neurogenic bladder, and other voiding difficulties [79].

When selecting diagnostic procedures to identify urolithiasis in children, it should be remembered that these patients might be uncooperative, require anaesthesia, and may be sensitive to ionising radiation. Again, the principle of ALARA (As Low As Reasonably Achievable) should be observed [80-84].

Ultrasound

Ultrasound is the primary imaging technique [85] in children. Its advantages are the 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 [80]. Colour Doppler US shows differences in the ureteral jet [86] and resistive index of the arciform arteries of both kidneys, which are indicative of the grade of obstruction [87]. Nevertheless, the US may fail to identify ureteral stones and provides limited information on renal function [88].

Plain films (KUB radiography)
Kidney-ureter-bladder radiography can help to identify stones and their radiopacity and facilitate follow-up.

Intravenous urography
The radiation dose for IVU is comparable to that for voiding cystourethrography (0.33 mSV) [89]. However, the need for contrast medium injection is a major drawback.

Non-contrast-enhanced computed tomography
Low-dose CT protocols have been shown to significantly reduce radiation exposure [90-92]. Sedation or anaesthesia is rarely needed with modern high-speed CT equipment.

Magnetic resonance urography
Magnetic resonance urography (MRU) 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 [93].

3.3.3.2.1 Summary of evidence and recommendations for diagnostic imaging in children

Summary of evidence	**LE**
Ultrasound is the first-line imaging modality in children when a stone is suspected; it should include the kidney, fluid-filled bladder, and the ureter next to the kidney and the (filled) bladder.	2b
A kidney-ureter-bladder radiography (or low-dose NCCT) is an alternative investigation if US will not provide the required information.	2b

Recommendations	**Strength rating**
Complete a metabolic evaluation based on stone analysis in all children.	Strong
Collect stone material for analysis to classify the stone type.	Strong
Perform ultrasound as first-line imaging modality in children when a stone is suspected; it should include the kidney, fluid-filled bladder, and the ureter.	Strong
Perform a kidney-ureter-bladder radiography (or low-dose non-contrast-enhanced computed tomography) if ultrasound will not provide the required information.	Strong

3.4 Disease Management

The treatment of urolithiasis is based on many parameters and is individualised for each patient. Parameters such as the size, number, location, and constitution of the stones are the cornerstones for deciding the treatment. In addition, the morphology, shape, volume, mobility, and hardness of the stone should be considered. Finally, the anatomy and compliance of the entire pelvic-calyceal system should be assessed for each patient. The design of therapeutic algorithms including all the above parameters is difficult mainly due to the great diversity of lithiasis disease per patient. Furthermore, there is a significant lack of comparative clinical studies to support development of algorithms using parameters other than stone size and composition.

3.4.1 Renal colic

Pain relief
Non-steroidal anti-inflammatory drugs (NSAIDs) (including metamizole dipyrone), and paracetamol are effective in patients with acute stone colic [94] and have better analgesic efficacy than opioids [95]. Ibuprofen compared to ketorolac is a more rapid-acting drug in controlling pain caused by renal colic with a similar side effect profile [96].

Pain relief from intramuscular (i.m.) diclofenac compared favourably with those from intravenous (i.v.) ibuprofen and i.v. ketorolac; however, no recommendation can be given due to the way in which the results have been reported [97]. The addition of antispasmodics to NSAIDs does not result in better pain control. 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 [94, 95]. Oral diclofenac in the long-term increases the risk of cardiovascular events and upper GI bleeding [98]. 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 [99]. Non-steroidal anti-inflammatory drugs may affect renal function in those patients with pre-existing decreased GFR.

In an RCT including 150 patients, Intradermal sterile water injection (ISWI) and diclofenac (i.m.) were shown equally effective for pain relief in acute renal colic. Intradermal sterile water injection may be an alternative to NSAIDs in pregnant patients or others where NSAIDs are contra-indicated [100].

Opioids, particularly pethidine, are associated with a high rate of vomiting compared to NSAIDs and carry a greater likelihood of further analgesia being needed [94, 101]. If an opioid is used, it is recommended that it is not pethidine. Combination of opioids and NSAIDs increase analgetic effect compared to opioids alone [102]. Acupuncture seems to be effective in renal colic alone or in combination with analgetic drugs, but there is limited data [103, 104].

Prevention of recurrent renal colic

Facilitation of passage of ureteral stones is discussed in Section 3.4.9. 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 [105, 106]. Although NSAID can affect renal function in patients with already reduced function, it has no functional effect in patients with normal renal function [107].

The systematic review and MA by Hollingsworth *et al.,* [108] addressed pain reduction as a secondary outcome and concluded that medical expulsive therapy (MET) seems efficacious in reducing pain episodes of patients with ureteral stones.

If analgesia cannot be achieved medically, drainage, using stenting, percutaneous nephrostomy, or stone removal, is indicated [109].

3.4.1.1 Summary of evidence and recommendations for the management of renal colic

Summary of evidence	**LE**
Non-steroidal anti-inflammatory drugs are very effective in treating renal colic and are superior to opioids.	1b
For symptomatic ureteral stones, stone removal as first-line treatment is a feasible option in selected patients.	1b

Recommendations	**Strength rating**
Offer a non-steroidal anti-inflammatory as the first drug of choice; depending on cardiovascular risk factors and side effects.	Strong
Offer opiates (hydromorphine, pentazocine or tramadol) as a second choice.	Weak
Offer renal decompression or ureteroscopic stone removal in case of analgesic refractory colic pain.	Strong

*3.4.2 **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

There are two options for urgent decompression of obstructed collecting systems [110]:

- placement of an indwelling ureteral stent
- percutaneous placement of a nephrostomy tube.

Several systematic reviews on the subject have been published, all of which emphasize that the available literature comparing different drainage modalities for obstructing stones with or without infection is scarce, based on small cohorts and of medium to very low quality [110]. There appears to be no difference in success rate or complication rate of both procedures and there is not a difference in time to defervescence in the population presenting with fever. Both meta-analyses identified patients receiving a nephrostomy tube to have a longer stay in the hospital. Based on the available data, a DJ stent has a more negative impact on the patients' quality of life in comparison with a nephrostomy tube, which can be explained mainly by the stent-related symptoms that these patients experience [111, 112].

Definitive stone removal should be delayed until the infection is cleared following a complete course of antimicrobial therapy. A small RCT showed the feasibility of immediate ureteroscopic stone removal combined

with an appropriate antibiotic regimen; however, at the cost of longer hospital stay and higher analgesic requirements [113].

Further measures
Along with 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 [114, 115]. The regimen should be re-evaluated in the light of the culture-antibiogram results. Although clinically well accepted, the impact of a second antibiogram test on treatment outcome has not yet been evaluated [116]. Intensive care might become necessary.

3.4.2.1 Summary of evidence and recommendations for the management of sepsis and anuria

Summary of evidence	**LE**
For decompression of the renal collecting system, ureteral stents and percutaneous nephrostomy catheters are equally effective.	1b

Recommendations	**Strength rating**
Urgently decompress the collecting system in case of sepsis with obstructing stones, using percutaneous drainage or ureteral stenting.	Strong
Delay definitive treatment of the stone until sepsis is resolved.	Strong
Collect (again) urine for antibiogram test following decompression.	Strong
Start antibiotics immediately (+ intensive care, if necessary).	Strong
Re-evaluate antibiotic regimen following antibiogram findings.	Strong

*3.4.3 **Medical expulsive therapy***
Several drug classes including α-blockers, calcium channel inhibitors, and phosphodiesterase type 5 inhibitors (PDEI-5) are used for MET [117-120] A class effect of α-blockers in MET has been demonstrated in MAs although this is an off-label indication [121-123]. However, there is contradictory evidence between these studies and several well-designed, multicentre, placebo-controlled, double-blinded randomised studies showing limited, or no, benefit using α-blockers, besides some advantage for distal ureteral stones > 5 mm [124-128]. Based on studies with a limited number of patients [120, 121, 129, 130], no recommendation for the use of PDEI-5 or corticosteroids in combination with α-blockers in MET can be made. The panel concludes that MET using α-blockers seems efficacious in the treatment of patients with distal ureteral stones > 5 mm who are amenable to conservative management. Medical expulsive therapy in special situations is addressed in the relevant chapters.

3.4.3.1 Summary of evidence and recommendations for medical expulsive therapy

Summary of evidence	**LE**
Medical expulsive therapy seems to be efficacious for treating patients with ureteral stones who are amenable to conservative management. The greatest benefit might be among those with > 5 mm (distal) ureteral stones.	1a
Insufficient data exist to support the use of PDEI-5 or corticosteroids in combination with α-blockers as an accelerating adjunct.	2a
Alpha-blockers increase stone expulsion rates in distal ureteral stones > 5 mm.	1a
A class effect of α-blockers has been demonstrated.	1a

Recommendation	**Strength rating**
Offer α-blockers as medical expulsive therapy as one of the treatment options for (distal) ureteral stones > 5 mm.*	Strong

** Alpha-blockers are an off-label treatment*

*3.4.4 **Chemolysis***

Percutaneous irrigation chemolysis

Percutaneous chemolysis is rarely used nowadays, for practical reasons. Percutaneous irrigation chemolysis may be an option for infection stones and theoretically also for uric acid stones. For dissolution of struvite stones, Suby's G solution (10% hemiacidrin; pH 3.5-4) can be used. The method has been described in case series and literature reviews [131].

Oral chemolysis

Stones composed of uric acid, but not sodium or ammonium urate stones, can be dissolved by oral chemolysis. Prior stone analysis may provide information on stone composition. Urinary pH measurement and X-ray characteristics can provide information on the type of stone.

Oral chemolysis is based on alkalinisation of urine by application of alkaline citrate or sodium bicarbonate. The pH should be adjusted to 7.0-7.2. Chemolysis is more effective at a higher pH, which might, however, promote calcium phosphate stone formation. Patients will need to adjust the dosage of alkalising medication by self-monitoring the pH of their urine. A SR shows a complete or partial dissolution in 80.5%, discontinuation rate of 10.2% with 15.7% requiring further intervention [132].

In the case of uric acid obstruction of the collecting system, oral chemolysis in combination with urinary drainage is indicated. A combination of alkalinisation with tamsulosin can increase the frequency of spontaneous passage of distal ureteral uric acid stones as shown in one RCT for stones > 5 mm [133]. Additional SWL might help to improve the results but evidence is weak [134].

3.4.4.1 Summary of evidence and recommendations for chemolysis

Summary of evidence	**LE**
Irrigation chemolysis has been used in limited clinical settings to dissolve struvite stones.	3
Uric acid stones > 5mm can be dissolved based on oral alkalinisation of the urine above 7.0.	3
For obstructing uric acid stones, a combination of oral chemolysis with tamsulosin is more effective than each substance alone, particularly in stones > 8 mm.	1b

Recommendations (oral chemolysis of uric acid stones)	**Strength rating**
Inform the patient how to monitor urine-pH by dipstick and to modify the dosage of alkalising medication according to urine pH, as changes in urine pH are a direct consequence of such medication.	Strong
Carefully monitor patients during/after oral chemolysis of uric acid stones.	Strong
Combine oral chemolysis with tamsulosin in case of (larger) ureteral stones (if active intervention is not indicated).	Weak

*3.4.5 **Extracorporeal shock wave lithotripsy (SWL)***

The success of SWL depends on the efficacy of the lithotripter and the following factors:

- size, location (ureteral, pelvic, or calyceal), and composition (hardness) of the stones (Section 3.4.9.3);
- patient's habitus (Section 3.4.10.3);
- performance of SWL (best practice, see below).

Each of these factors significantly influences the retreatment rate and outcome of SWL.

Best clinical practice

Stenting

Routine use of internal stents before SWL does not improve stone-free rates (SFRs), nor lowers the number of auxiliary treatments. It may, however, reduce the formation of steinstrasse [135-138].

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 [139].

Shock wave rate

Lowering shock wave frequency from 120 to 60-90 shock waves/min improves SFRs [140-148]. Ultraslow

frequency of 30 shock waves/min may increase SFR [149]. Tissue damage increases with shock wave frequency [150-153].

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 [154]. Starting SWL on a lower energy setting with stepwise power (and SWL sequence) ramping can achieve vasoconstriction during treatment [150], which prevents renal injury [155-157]. Animal studies [158] and a prospective randomised study [159] 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 [160, 161].

There are no conclusive data on the intervals required between repeated SWL sessions. However, clinical experience indicates that repeat sessions are feasible (within one day for ureteral stones) [162].

Improvement of acoustic coupling
Proper acoustic coupling between the cushion of the treatment head and the patient's skin is important. Defects (air pockets) in the coupling gel deflect 99% of shock waves [163]. Gentle swiping between the coupled therapy head and the patient skin helps remove air bubbles and improves the coupling [164]. Ultrasound gel is probably the most widely-used agent available as a lithotripsy coupling agent [165].

Procedural control
Results of treatment are operator-dependent, and experienced clinicians obtain better results. During the procedure, careful imaging control of localisation contributes to outcome quality [166].

Pain Control
Careful control of pain during treatment is necessary to limit pain-induced movements and excessive respiratory excursions [167-170].

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) [62, 171, 172].

Medical therapy after extracorporeal shock wave lithotripsy
Despite conflicting results, most RCTs and several MAs support MET after SWL for ureteral or renal stones as an adjunct to expedite expulsion and increase SFRs. Medical expulsion therapy might also reduce analgesic requirements [173].

Post-treatment management
Mechanical percussion and diuretic therapy can significantly improve SFRs and accelerate stone passage after SWL [174].

Complications of extracorporeal shock wave lithotripsy
Compared to percutaneous nephrolithotomy (PCNL) and ureteroscopy (URS), there are fewer overall complications with SWL [175] (Table 3.8). In a Meta-Analysis of 115 RCT´s 18.43% of Clavien I–II complications and 2.48% of Clavien III–IV complications occurred [175]. 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 [176-182].

Table 3.8: Shock wave lithotripsy-related complications

Complications			**%**	**Reference**
Related to stone fragments	Steinstrasse		4	[183-185]
	Macroscopic haematuria		17.2%	[175]
	Pain		12.1%	[175]
	Regrowth of residual fragments		21 – 59	[186, 187]
	Auxiliary procedure		6.9%	[175]
	Renal colic		2 – 4	[188]

Infectious	Bacteriuria in non-infection stones		7.7 – 23	[186-189]
	Sepsis		0.15%	[175]
Tissue effect	Renal	Haematoma, symptomatic	0.21%	[175]
		Haematoma, asymptomatic	1.2%	[175]
	Cardiovascular	Dysrhythmia	11 – 59	[186, 188]
		Morbid cardiac events	Case reports	[186, 188]
	Gastrointestinal	Bowel perforation	Case reports	[190]
		Liver, spleen haematoma	Case reports	[190-193]

3.4.5.1 Summary of evidence and recommendations for Shock wave lithotripsy

Summary of evidence	**LE**
Stepwise power ramping prevents renal injury.	1b
Clinical experience has shown that repeat sessions are feasible (within one day for ureteral stones).	4
Optimal shock wave frequency is 1.0 to 1.5 Hz.	1a
Proper acoustic coupling between the cushion of the treatment head and the patient's skin is important.	2
Careful imaging control of localisation of stone contributes to outcome of treatment.	2a
Careful control of pain during treatment is necessary to limit pain-induced movements and excessive respiratory excursions.	1a
Antibiotic prophylaxis is recommended in the case of internal stent placement, infected stones, or bacteriuria.	1a

Recommendations	**Strength rating**
Ensure correct use of the coupling agent because this is crucial for effective shock wave transportation.	Strong
Maintain careful fluoroscopic and/or ultrasonographic monitoring during shock wave lithotripsy (SWL).	Strong
Use proper analgesia because it improves treatment results by limiting pain-induced movements and excessive respiratory excursions.	Strong
Prescribe antibiotics prior to SWL in the case of infected stones or bacteriuria.	Strong

3.4.6 ***Ureteroscopy (retrograde and antegrade)***

The current standard for rigid ureteroscopes is a tip diameter of < 8 French (F). Rigid URS can be used for the whole ureter [176]. However, technical improvements, as well as the availability of digital scopes, also favour the use of flexible ureteroscopes in the ureter [194].

Percutaneous antegrade removal of ureteral stones is a consideration in selected cases, i.e. large (> 15 mm), impacted proximal ureteral calculi in a dilated renal collecting system [195, 196], or when the ureter is not amenable to retrograde manipulation [197].

Ureteroscopy for renal stones: Retrograde Intrarenal Surgery (RIRS)

Technical improvements including endoscope miniaturisation, improved deflection mechanism, enhanced optical quality and tools, and introduction of disposables have led to an increased use of URS for both renal and ureteral stones. Major technological progress has been achieved for RIRS. A systematic review addressing renal stones > 2 cm showed a cumulative SFR of 91% with 1.45 procedures/patient; 4.5% of the complications were > Clavien 3 [198, 199]. Digital scopes demonstrate shorter operation times due to the improvement in image quality [200].

Stones that cannot be extracted directly must be disintegrated. If it is difficult to access stones within the lower renal pole that need disintegration it may help to displace them into a more accessible calyx [201].

Best clinical practice in ureteroscopy

Access to the upper urinary tract

Most interventions are performed under general anaesthesia, although local or spinal anaesthesia is possible [202]. Intravenous sedation is suitable for female patients with distal ureteral stones [203]. Smaller caliber (4.5/6 Fr) semi-rigid ureteroscope was associated with significantly higher SFR, lower rates of ureteric injury, and shorter hospital stay [204].

Antegrade URS is an option for large, impacted, proximal ureteral calculi [195, 205]. Reduction of flexible ureteroscope diameter may provide similar vision, deflection, and manoeuvrability to standard flexible ureteroscopes potentially with improved ureteric access [206]. Disposable ureteroscopes provide similar safety and clinical effectiveness to reusable scopes. Concerns regarding cost-effectiveness and environmental sustainability remain [204, 207-209].

Safety aspects

Fluoroscopic equipment must be available in the operating room. The Panel recommends placement of a safety wire, even though some groups have demonstrated that URS can be performed without it [210-214]. Balloon and plastic dilators should be available, if necessary.

Prior rigid URS can be helpful for optical dilatation followed by flexible URS, if necessary. If ureteral access is not possible, insertion of a JJ stent followed by URS after seven to fourteen days offers an alternative [215]. Bilateral URS during the same session is feasible resulting in equivalent-to-lower SFRs, but slightly higher overall complication rates (mostly minor, Clavien 1 and 2) [216, 217].

Difficult lower pole anatomy such as steep infundibulopelvic angle predisposes to failure during RIRS [218]. A reusable flexible ureteroscope can be more helpful in reaching a difficult lower pole calyx [219]. Prolonged operative times are linked to increased complication rates in ureteroscopy, and efforts must be made to keep it below 90 minutes [220].

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 UUT and therefore significantly facilitate URS. The use of ureteral access sheaths improves vision by establishing a continuous outflow, decreases intrarenal pressure, and potentially reduces operating time [221, 222].

The insertion of ureteral access sheaths may lead to ureteral damage, the risk is lowest in pre-stented systems [223]. No data on long-term side effects are available [198, 223]. Whilst larger cohort series showed no difference in SFRs and ureteral damage (stricture rates of about 1.8%), they did show lower post-operative infectious complications [224, 225]. Increasing sheath size directly determines higher grades of ureteral injury rates but there is no difference in long-term stricture rates [226]. The use of a ureteral access sheath is safe and can be useful for large and multiple renal stones or if long procedural time is expected [227].

Stone extraction

The aim of URS is complete stone removal. “Dust and go” strategies should be limited to the treatment of large (renal) stones [228]. Stones can be extracted by endoscopic forceps or baskets. Only baskets made of nitinol can be used for flexible URS [229].

Intracorporeal lithotripsy

The most effective lithotripsy system is the holmium: yttrium-aluminum-garnet (Ho: YAG) laser, which is currently the optimum standard for URS and flexible nephroscopy (Section 3.4.6), because it is effective in all stone types [230, 231]. Compared to low-power lasers, high-power laser reduces procedural time although the reported difference in clinical outcomes was non-significant and based on a low level of evidence [232]. The only RCT to date shows no clinical difference regarding stone-free rate or operative time [233]. Although pulse-modulation in Ho: YAG lasers has demonstrated several in vitro benefits, a systematic review including 8 comparative studies and only one RCT showed no difference in stone-free rate, complication rate, or operative time [234]. The two available RCTs on the subject both found a shorter operative time, without conferring a difference in success rate [235, 236]. Thulium fiber laser (TFL) for stone disease has a promising role and offers good clinical outcomes, which seem to be comparable to Ho: YAG laser (holmium) laser [237-239]. With the limited reports of clinical use available to date, a meta-analysis could not demonstrate the superiority of TFL over Ho: YAG, although the operative time to achieve this stone-free rate seems to be shorter with the use of TFL [240]. More comparative clinical studies are however needed between these two modalities. When a laser is not available, pneumatic and US systems can be used with high disintegration efficacy in rigid URS [241, 242]. However, stone migration into the kidney is a common problem, which can be prevented by the placement

of special anti-migration tools proximal to the stone [243]. Medical expulsion therapy following Ho: YAG laser lithotripsy increases SFRs and reduces colic episodes [244].

Stenting before and after URS

Routine stenting is not necessary before URS. Despite a complete lack of RCTs on this subject, a meta-analysis has been performed, demonstrating that pre-stenting may improve the stone-free rate of ureteroscopic treatment of renal stones, but not of ureteral stones [245]. Although it may facilitate ureteroscopic management of stones and increase success in access sheath placement, intra-operative complications were not significantly different [245, 246]. One should also consider that pre-stenting also causes the patient to experience stent-related symptoms during the time the stent is indwelling, prior to a procedure.

Randomised prospective trials have found that routine stenting after uncomplicated URS (complete stone removal) is not necessary; stenting might be associated with higher postoperative morbidity and costs [247]. Smaller diameter ureteric stents may reduce urinary symptoms and patient-reported pain [248]. A ureteral catheter with a shorter indwelling time (one day) may also be used, with similar results [249].

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 one to two weeks after URS. Alpha-blockers reduce the morbidity of ureteral stents and increase tolerability [250].

Medical expulsive therapy before and after ureteroscopy

Medical expulsion therapy before URS might reduce the risk for intra-operative ureteral dilatation, protect against ureteral injury when using access sheaths and increase stone-free rates four weeks after URS [251, 252].

Medical expulsion therapy following Ho: YAG laser lithotripsy accelerates the spontaneous passage of fragments and reduces episodes of colic [244].

Complications of ureteroscopy

The overall complication rate after URS is 4-25% [253, 254]. Most complications are minor and do not require intervention. There is evidence suggesting a risk of post-operative urosepsis of up to 5% [255, 256]. Ureteral avulsion and strictures are rare (< 1%). Previous perforations, pre-operative positive urine cultures, comorbidities, and longer operation time are the most important risk factor for complications [220, 257, 258]. Infectious complications following URS can be minimised using prophylactic antibiotics, limiting stent dwell and procedural time, identification and treatment of UTI, and planning in patients with large stone burden and multiple comorbidities [259].

High intrarenal pressure (IRP) predisposes to URS complications, and measures should be used to reduce IRP. Currently, there are no accurate ways to measure the intra-operative IRP [260].

3.4.6.1 Summary of evidence and recommendations for retrograde URS, RIRS and antegrade ureteroscopy

Summary of evidence	**LE**
In uncomplicated URS, a post-procedure stent need not be inserted.	1a
In URS, pre-stenting has been shown to improve outcomes for renal stones.	1a
An α-blocker can reduce stent-related symptoms and colic episodes.	1a
The most effective lithotripsy system for flexible ureteroscopy is the Ho: YAG laser.	2a
Pneumatic and US systems can be used with high disintegration efficacy in rigid URS.	2a
Percutaneous antegrade removal of proximal ureter stones, or laparoscopic ureterolithotomy are feasible alternatives to retrograde ureteroscopy, in selected cases.	1b
Pre-treatment of patients undergoing URS with an α-blocker one week prior to the procedure reduces the need for active dilatation and increases the stone free rate.	1a

Recommendations	**Strength rating**
Use holmium: yttrium-aluminum-garnet (Ho: YAG) or Thulium fiber laser (TFL) laser lithotripsy for (flexible) ureteroscopy (URS).	Strong
Perform stone extraction only under direct endoscopic visualisation of the stone.	Strong

Do not insert a stent in uncomplicated cases.	Strong
Offer medical expulsive therapy for patients suffering from stent-related symptoms and after Ho: YAG laser lithotripsy to facilitate the passage of fragments.	Strong
Use percutaneous antegrade removal of ureteral stones as an alternative when shock wave lithotripsy (SWL) is not indicated or has failed, and when the upper urinary tract is not amenable to retrograde URS.	Strong
Use flexible URS (even for stones > 2 cm) in cases where percutaneous nephrolithotomy or SWL are not an option. However, in this case, there is a higher risk that a follow-up procedure and placement of a ureteral stent may be needed.	Strong

*3.4.7 **Percutaneous nephrolithotomy***

Percutaneous nephrolithotomy 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 reference. Standard access tracts are 24-30 F. Smaller access sheaths, < 18 F, were initially introduced for paediatric use, but are now increasingly utilized in the adult population [261, 262].

Contraindications

Patients receiving anticoagulant therapy must be monitored carefully pre-and post-operatively. Anti-coagulant therapy must be discontinued before PCNL [263].

Other important considerations include:

- untreated UTI;
- tumour in the presumptive access tract area;
- potential malignant kidney tumour;
- pregnancy (Section 3.4.14.1).

Best clinical practice

Intracorporeal lithotripsy

Several methods for intracorporeal lithotripsy during PCNL are available. Ultrasonic, pneumatic, and combined systems are most commonly used for rigid nephroscopy, whilst the laser is increasingly used for miniaturised and flexible instruments [264].

Pre-operative imaging

Pre-procedural imaging evaluations are summarised in Section 3.3.1. In particular, US or CT of the kidney and the surrounding structures can provide information regarding interposed organs within the planned percutaneous path (e.g., spleen, liver, large bowel, pleura, and lung).

Positioning of the patient

Both prone and supine positions are equally safe. A meta-analysis including twelve studies and a total of 1,290 patients treated, showed a similar SFR but a lower operative time for supine PCNL [265]. The supine position allows simultaneous retrograde access to the collecting system, using a flexible ureteroscope [266]. The combination of PCNL and RIRS may be a good alternative for the treatment of complex renal stones compared to standard PCNL; however, the existing evidence is of low-quality [265, 267].

Puncture

Although fluoroscopy is still the most common intra-operative imaging method, the use of US as an additional or only means of puncture guidance provides advantages according to two meta-analyses including eight randomised controlled trials. Additional to the expected reduced radiation exposure with the use of ultrasound the meta-analyses also demonstrated a lower complication rate [268, 269]. Pre-operative CT or intra-operative US allows identification of the tissue between the skin and kidney and lowers the incidence of visceral injury. As an additional aid to increase puncture accuracy, the calyceal puncture may be done under direct visualisation using simultaneous flexible URS [270-272].

Dilatation

Dilatation of the percutaneous access tract can be achieved using a metallic telescopic, single (one-shot or serial) dilator, or balloon dilatator. During PCNL, safety and effectiveness are similar for different tract dilatation methods [273]. Although there are papers demonstrating that single-step dilation is equally effective as other methods and that US only can be used for the dilatation, the difference in outcomes is most likely related to surgeon experience rather than to the technology used [273, 274]. A meta-analysis of the most commonly used

tract dilation methods suggested that one-step dilation would allow for a shorter operative time and reduced complication rate, including haemoglobin loss and transfusion rate [275].

Choice of instruments

Several meta-analyses on mini-PCNL (12-22 F) vs. standard PCNL (> 22 F) have identified that both techniques allow for a similar SFR. Patients treated with mini-PCNL had reduced blood loss and transfusion rates, as well as a shorter hospital stay, without a significant difference in overall complication rates [262, 276-278]. However, it is important to note that the level of evidence was downgraded due to heterogeneity of data related to tract sizes used and types of stones treated. There is some evidence for using suction during PCNL to reduce intra-renal pressure and increase SFR [279].

Post-operative drainage

The decision on whether, or not, to place a nephrostomy tube or a double J stent at the conclusion of the PCNL procedure depends on several factors, including:

- presence of residual stones;
- likelihood of a second-look procedure;
- significant intra-operative blood loss/ bleeding from the percutaneous tract;
- 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 postoperative pain [262, 280, 281]. Tubeless PCNL is performed without a nephrostomy tube and is associated with reduced post-operative pain and hospital stay [282]. When neither a nephrostomy tube nor a ureteral stent is introduced, the procedure is known as a totally tubeless PCNL [283]. In uncomplicated cases, the latter procedure results in a shorter hospital stay, with no disadvantages reported [284].

As reported in the above section on the drainage of an infected or obstructed system [110-112] (section 3.4.2), the quality of life may be slightly lower with a DJ stent in comparison to a short-term nephrostomy tube after PCNL. This should be weighed against the shorter hospital stay with a DJ stent [285].

Complications of percutaneous nephrolithotomy

A systematic review of almost 12,000 patients shows the incidence of complications associated with PCNL; fever 10.8%, transfusion 7%, thoracic complication 1.5%, sepsis 0.5%, organ injury 0.4%, embolisation 0.4%, urinoma 0.2%, and death 0.05% [286].

Perioperative 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. The evidence demonstrates that a stone culture or urine culture taken directly from the renal pelvis is more predictive of post-operative SIRS or sepsis. Whenever possible a urine culture from the renal pelvis and/or stone culture should be taken at the time of PCNL [287].

Intra-operative renal stone or renal pelvic urine culture may be more indicative of the causative organism for sepsis; therefore, helping to select the most suitable postoperative antibiotics [287-289]. Although this data is weak, there is limited retrospective data indicating that increased pressures during mPCNL may contribute to febrile complications [290-292]. This contrasts with the previously mentioned meta-analyses on mini vs standard PCNL that do not identify a difference in complication rate between the two procedures [262, 276-278]. Bleeding after PCNL may be treated by briefly clamping the nephrostomy tube. Super-selective embolic occlusion of the arterial branch may become necessary in the case of severe bleeding. Several meta-analyses have demonstrated that the use of tranexamic acid reduces bleeding complications and the transfusion rate of PCNL [293-295]. However, the transfusion rate in the control group of the meta-analyses was in the range of 10-12%.

Depending on the stone burden and the patient's anatomy, multiple tracts may be necessary to render the patient stone free in one session of PCNL. While this is a generally accepted practice, it should be highlighted that this comes with an increased risk of postoperative complications including pleural damage, infections, and the need for transfusion [296].

To reduce post-operative pain after PCNL, a peripheral nerve block can be performed at the intercostal nerve, paravertebral region, erector spinae, or quadratus lumborum. Such a block may significantly reduce the need for post-operative opioid analgesics [297, 298]. Current evidence shows that a quadratus lumborum block or

infiltration of a local anaesthetic around the nephrostomy tube may reduce post-operative pain and opioid consumption after PCNL [299, 300].

3.4.7.1 Summary of evidence and recommendations for endourology techniques for renal stone removal

Summary of evidence	LE
Imaging of the kidney with US or CT can provide information regarding inter-positioned organs within the planned percutaneous path (e.g., spleen, liver, large bowel, pleura, and lung).	3
Both prone and supine positions are equally safe with equivalent SFR.	1a
Percutaneous nephrolithotomy performed with small instruments tends to be associated with significantly lower blood loss, but the duration of procedure tended to be significantly longer. There are no significant differences in SFR or any other complications.	1a
In uncomplicated cases, a totally tubeless PCNL results in a shorter hospital stay, with no increase in complication rate.	1a
Peri-operative use of tranexamic acid may reduce bleeding complications and transfusion rates.	1a
Urine cultures taken directly from the renal pelvis, or a stone culture are more predictive of post-PCNL sepsis than a pre-operative midstream urine culture.	1a

Recommendations	Strength rating
Perform pre-procedural computed tomography (CT) imaging, including contrast medium when indicated 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.	Strong
Perform a tubeless (without nephrostomy tube) or totally tubeless (without nephrostomy tube and ureteral stent) percutaneous nephrolithotomy (PCNL) procedure, in uncomplicated cases.	Strong
Take a stone culture or urine culture directly from the renal pelvis at time of PCNL, if possible.	Strong

*3.4.8 **General recommendations and precautions for stone removal***

3.4.8.1 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 before starting stone removal. A urine culture or urinary microscopy should be performed before treatment [301].

Peri-operative antibiotic prophylaxis

The available evidence for prevention of infection following URS and percutaneous stone removal, remains limited [302]. Administration of a single dose of prophylactic antibiotics prior to ureteroscopy was found to be sufficient [302-304]. In a review of a large database of patients undergoing PCNL, it was found that in patients with negative baseline urine culture, antibiotic prophylaxis significantly reduced the rate of postoperative fever and other complications [305]. Based on three meta-analyses, pooling data from small series with varying quality an extended course of pre-operative prophylactic antibiotics prior to PCNL compared to a single dose before anaesthesia significantly reduced post-operative sepsis and fever in patients with an a priori increased risk of infection [288, 306, 307]. In an RCT including only moderate to high-risk infection patients (patients with pre-operative stents/nephrostomy or positive urine culture), a seven-day course of pre-operative antibiotics reduced the risk of post-PCNL sepsis threefold in comparison to a two-day course [308]. In studies that did not specify the risk of the patient population, a single dose of antibiotic prophylaxis administered at induction was equivalent to an extended pre-operative course [307, 309]. In contrast to this, a prolonged course of post-operative antibiotics was not superior to a single dose pre-operatively [288, 307].

As national and regional antibiotic resistance patterns can differ significantly, the choice of antibiotic prophylaxis should be tailored to institutional or regional antimicrobial susceptibility [304].

Recommendations	Strength rating
Obtain a urine culture or perform urinary microscopy before any treatment is planned.	Strong
Exclude or treat urinary tract infections prior to stone removal.	Strong
Offer peri-operative antibiotic prophylaxis to all patients undergoing endourological treatment.	Strong

3.4.8.2 Antithrombotic therapy and stone treatment

Patients with a bleeding disorder, or receiving antithrombotic therapy, should be referred to an internist for appropriate therapeutic measures before deciding on stone management [310-314]. In patients with an uncorrected bleeding disorder, the following are at elevated risk of haemorrhage or perinephric haematoma (PNH) (high-risk procedures):

- SWL (hazard ratio of PNH up to 4.2 during anti-coagulant/anti-platelet medication) [315]
- PCNL;
- percutaneous nephrostomy;
- laparoscopic surgery;
- open surgery [310].

Shock wave lithotripsy is feasible and safe after correction of the underlying coagulopathy [316, 317]. In the case of an uncorrected bleeding disorder or continued antithrombotic therapy, URS, in contrast to SWL and PCNL, might offer an alternative approach since it is associated with less morbidity [318-320]. Despite the appropriate cessation of anti-platelet agents, following standardised protocols, prolonged haematuria in tube drainage after PCNL has been reported [321]. Only data on flexible URS are available which support the superiority of URS in the treatment of proximal ureteral stones [322, 323]. Although URS is safe in patients with bleeding disorders or anticoagulation, an individualised patient approach is necessary [320].

Table 3.9: Risk stratification for bleeding [312-314, 324]

Low-risk bleeding procedures	• Cystoscopy • Flexible cystoscopy • Ureteral catheterisation • Extraction of ureteral stent • Ureteroscopy
High-risk bleeding procedures	• Shock wave lithotripsy • Percutaneous nephrostomy • Percutaneous nephrolithotomy

Table 3.10: Suggested strategy for antithrombotic therapy in stone removal [312-314]
(In collaboration with a cardiologist/internist weigh the risks and benefits of discontinuation of therapy, vs. delaying elective surgical procedures).

Medication/Agent	Bleeding risk of planned procedure	Risk of thromboembolism		
		Low risk	Intermediate risk	High risk
Warfarin Dabigatran Rivaroxaban Apixaban	Low-risk procedure	May be continued	Bridging therapy	Bridging therapy
	High-risk procedure	May be temporarily discontinued at appropriate interval. Bridging therapy is strongly recommended.	Bridging therapy	Bridging therapy

Aspirin	Low-risk procedure	Continue	Continue	Elective surgery: postpone. Non-deferrable surgery: continue.
	High-risk procedure	Discontinue	Elective surgery: postpone. Non-deferrable surgery: continue, if it is possible.	Elective surgery: postpone. Non-deferrable surgery: continue.
Thienopyridine agents (P2Y12 receptor inhibitors)	Low-risk procedure	Discontinue five days before intervention. Resume within 24-72 hours with a loading dose.	Continue	Elective surgery: postpone. Non-deferrable surgery: continue.
	High-risk procedure	Discontinue five days before intervention and resume within 24-72 hours with a loading dose.	Elective surgery: postpone. Non-deferrable surgery: discontinue five days before procedure and resume within 24-72 hours with a loading dose. Bridging therapy -glycoprotein IIb/IIIa inhibitors if aspirin is discontinued.	Elective surgery: postpone. Non-deferrable surgery: discontinue five days before procedure and resume within 24-72 hours, with a loading dose. Bridging therapy -glycoprotein IIb/IIIa inhibitors.

3.4.8.2.1 Summary of evidence and recommendations for antithrombotic therapy and stone treatment

Summary of evidence	**LE**
Active surveillance is indicated in patients at high risk for thrombotic complications in the presence of an asymptomatic calyceal stone.	4
The temporary discontinuation, or bridging of antithrombotic therapy in high-risk patients, should be discussed with the internist.	3
Retrograde (flexible) URS stone removal is associated with less morbidity in patients when antithrombotic therapy cannot be discontinued.	2a

Recommendations	**Strength rating**
Offer active surveillance to patients at high risk of thrombotic complications in the presence of an asymptomatic calyceal stone.	Weak
Decide on temporary discontinuation, or bridging of antithrombotic therapy in high-risk patients, in consultation with the internist.	Strong
Retrograde (flexible) URS is the preferred intervention if stone removal is essential and antithrombotic therapy cannot be discontinued since it is associated with less morbidity.	Strong

3.4.8.3 Obesity

A high BMI can pose a higher anaesthetic risk and a lower success rate after SWL and PCNL and may influence the choice of treatment [325].

3.4.8.4 Stone composition

Stones composed of brushite, calcium oxalate monohydrate, or cystine are particularly hard, as well as homogeneous stones with a high density on NCCT [326, 327]. Percutaneous nephrolithotomy or RIRS and URS are alternatives for removal of large SWL-resistant stones.

Recommendations	Strength rating
Consider the stone composition before deciding on the method of removal, based on patient history, former stone analysis of the patient or Hounsfield unit on unenhanced computed tomography.	Strong
Attempt to dissolve radiolucent stones.	Strong

3.4.8.5 Contraindications of procedures

Contraindications of extracorporeal SWL

There are several contraindications to the use of extracorporeal SWL, including:

- pregnancy, due to the potential effects on the foetus [328];
- bleeding disorders, which should be compensated for at least 24 hours before and 48 hours after treatment [329];
- uncontrolled UTIs;
- severe skeletal malformations and severe obesity, which prevent targeting of the stone;
- arterial aneurysm in the vicinity of the stone [330];
- anatomical obstruction distal to the stone.

Contraindications of URS

Apart from general problems, for example with general anaesthesia or untreated UTIs, URS can be performed in all patients without any specific contraindications.

Contraindications of PCNL

Patients receiving anti-coagulant therapy must be monitored carefully pre- and post-operatively. Anti-coagulant therapy must be discontinued before PCNL [320]. Other important contraindications include:

- untreated UTI;
- tumour in the presumptive access tract area;
- potential malignant kidney tumour;
- pregnancy (Section 3.4.14.1).

General contraindication for endourological procedures

Endourological interventions do not adversely affect renal function although care must be taken in those with poor pre-operative renal function, diabetes and hypertension [331]. However, a meta-analysis, based on low quality evidence, suggests that patients with impaired renal function and stone disease, may in fact benefit from the procedure to preserve or increase their renal function [332].

3.4.9 ***Specific stone management of ureteral stones***

3.4.9.1 Conservative treatment/observation

There are only limited data regarding spontaneous stone passage according to stone size [333, 334].

Spontaneous stone passage was reported for 49-52% of upper ureteral stones, 58-70% of mid ureteral stones and 68-83% of distal ureteral stones. Considering stone size almost 75% of stones < 5 mm and 62% of stones ≥ 5 mm passed spontaneously, with an average time to stone expulsion about 17 days (range 6-29 days) [333, 335]. Considering both size and location, stones of <5mm in the distal ureteral have a 89% chance of spontaneous passage, while 71% of stones <5mm located in the upper ureter still pass spontaneously [333]. The Panel is aware of the fact that spontaneous stone expulsion decreases with increasing stone size and that there are differences between individual patients.

3.4.9.2 Pharmacological treatment, medical expulsive therapy

Medical expulsive therapy should only be used in informed patients if active stone removal is not indicated. Treatment should be discontinued if complications develop (infection, refractory pain, deterioration of renal function). In the case of known uric acid stones in the distal ureter, a combination of alkalinisation with tamsulosin can increase the frequency of spontaneous passage. For details see Sections 3.4.3 and 3.4.4.

3.4.9.3 Indications for treatment of ureteral stones

Indications for removal of ureteral stones are [176, 334, 336]:

- stones with a low likelihood of spontaneous passage;
- persistent pain despite adequate analgesic medication;
- persistent obstruction;
- renal insufficiency (renal failure, bilateral obstruction, or single kidney).

3.4.9.4 Selection of procedure for removal of ureteral stones

The selection of the procedure depends on many factors, including stone-related factors, such as size, location, and density, as well as patient-related factors, such as body habitus, urinary anatomy, bleeding disorders, and other potential comorbidities. These and their influence on the outcomes of each of the procedures should be considered when counselling patients.

As previously mentioned in this guideline, CT imaging can provide useful information that may influence the choice of treatment. A meta-analysis outlines that increasing stone density, stone burden, skin-to-stone distance, and hydronephrosis can negatively impact the success of the shockwave lithotripsy [337].

Overall, SFRs after URS or SWL for ureteral stones are comparable. However, larger stones achieve earlier stone-free status with URS.

A large multi-center non-inferiority trial compared URS to SWL for ureteral stones. When excluding patients that had spontaneously passed their stone prior to treatment, SWL could not be considered non-inferior to URS with only 12% of patients needing further intervention after URS in comparison to 26% in the SWL arm [253]. In contrast to the success of SWL, comparative data on the outcomes of URS depending on patients' BMI has shown URS to be as effective and safe in obese and morbidly obese patients as in non-obese patients [338].

The Panel performed a systematic review to assess the benefits and harms of URS compared to SWL [339]. Compared with SWL, URS was associated with a significantly greater SFR of up to four weeks, but the difference was not significant at three months in the included studies. Ureteroscopy was associated with fewer retreatments and the need for secondary procedures but with a higher need for adjunctive procedures, higher complication rates, and longer hospital stay. Counterbalancing for URS's higher SFRs, SWL is associated with lower morbidity. Success rates and complications of URS are not impacted by previous unsuccessful SWL [340]. Clavien-Dindo grade complications were if reported, less frequent in patients treated with SWL [175].

Apart from the treatment modality, the timing of treatment may also be of importance. Primary or emergent ureteroscopy appears to be a safe and feasible procedure for patients presenting with renal colic due to an obstructive ureteral stone [341], without however increasing the stone-free rate. These results however are based mainly on low level of evidence reports and should be interpreted with caution [341]. Similarly, SWL can be performed in the acute setting or electively allowing a trial of spontaneous passage. In contrast to acute URS, SWL in the acute setting does provide an increased stone-free rate and reduced need for auxiliary procedures [342].

For large proximal ureteral stones, a percutaneous antegrade approach may provide better stone-free results than a retrograde ureteroscopic approach [343].

Bleeding disorder

Ureteroscopy can be performed in patients with bleeding disorders, with a moderate increase in complications (see also Section 3.4.8.2) [320].

3.4.9.4.1 Summary of evidence and recommendations for selection of procedure for active removal of ureteral stones

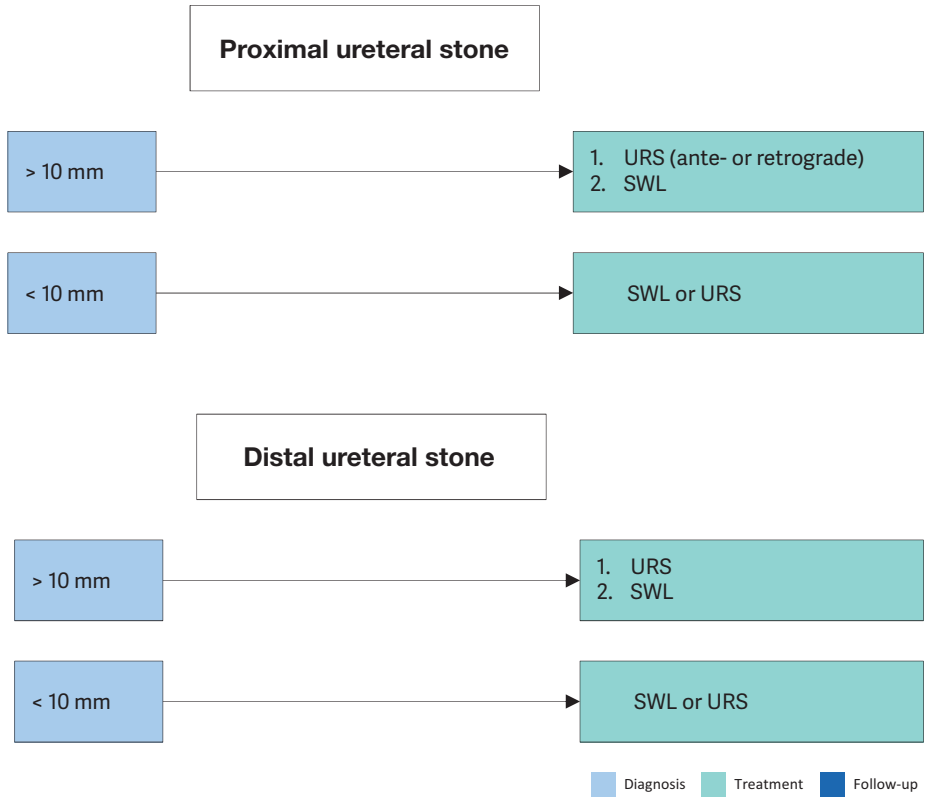
Summary of evidence	**LE**
Observation is feasible in informed patients who develop no complications (infection, refractory pain, deterioration of renal function).	2a
Medical expulsive therapy seems to be efficacious for treating patients with ureteral stones who are amenable to conservative management. The greatest benefit might be among those with > 5 mm (distal) stones.	1a
Compared with SWL, URS was associated with significantly greater SFRs up to four weeks, but the difference was not significant at three months in the included studies.	1a
Ureteroscopy was associated with fewer retreatments and need for secondary procedures, but with a higher need for adjunctive procedures, greater complication rates and longer hospital stay.	1a
In the case of severe obesity, URS is a more promising therapeutic option than SWL.	2b

Recommendations	Strength rating
If active removal is not indicated (Section 3.4.9.3) in patients with newly diagnosed small* ureteral stones, observe patient initially with periodic evaluation.	Strong
Offer α-blockers as medical expulsive therapy as one of the treatment options for (distal) ureteral stones > 5 mm**.	Strong
Inform patients that ureteroscopy (URS) has a better chance of achieving stone-free status with a single procedure.	Strong
Inform patients that URS has higher complication rates when compared to shock wave lithotripsy.	Strong
Use URS as first-line therapy for ureteral (and renal) stones in cases of severe obesity.	Strong

**See stratification data [176].*

*** Alpha-blockers are an off-label treatment for this indication*

Figure 3.1: Treatment algorithm for ureteral stones (if stone removal is indicated)



SWL = shock wave lithotripsy; URS = Ureteroscopy.

3.4.10 Specific stone management of 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. In an RCT patients with small asymptomatic renal stones, who were not treated actively, had a higher incidence of relapse [344].

3.4.10.1 Conservative treatment (observation)

Observation of renal stones, especially in calyces, depends on their natural history (Section 3.4.10.3). The recommendations provided are not supported by high-level literature [345]. There is a prospective trial supporting annual observation for asymptomatic inferior calyceal stones, < 10 mm. In case stone growth is detected, the follow-up interval should be lowered [346]. Intervention is advised for growing stones > 5 mm [347]. In a systematic review of patients with asymptomatic renal stones on active surveillance spontaneous stone passage rates varied from 3-29%, symptom development from 7-77%, stone growth from 5-66%, surgical intervention from 7-26% [345].

3.4.10.2 Pharmacological treatment of renal stones

Dissolution therapy seems to be an option for uric acid stones. See sections 3.4.4. and 3.4.8.4.

3.4.10.3 Indications for stone removal of renal stones

Indications for the removal of renal stones include:

- stone growth;
- stones in high-risk patients for stone formation;
- obstruction caused by stones;
- infection;
- symptomatic stones (e.g., pain or haematuria) [348];
- patient preference;
- comorbidity;
- the social situation of the patient (e.g., profession or traveling);

3.4.10.4 Selection of procedure for active removal of renal stones

For general recommendations and precautions see Section 3.4.8.

3.4.10.4.1 Stones in the renal pelvis or upper/middle calyces

Shock wave lithotripsy, PCNL and RIRS are available treatment modalities for renal calculi. While PCNL efficacy is hardly affected by the stone size, the SFRs after SWL or URS are inversely proportional to stone size [253, 349-355]. Although multiple treatments or sessions may be needed shock wave lithotripsy achieves good SFRs for stones up to 20 mm, except for those at the lower pole [351, 356, 357]. When SWL is considered, stones with density > 1,000 HU (and with high homogeneity) on non-contrast-enhanced CT are less likely to be disintegrated [43]. Endourology is considered an alternative because of the reduced need for repeated procedures and consequently a shorter time until stone-free status is achieved. For stones > 10 mm, mPCNL achieves a higher SFR than RIRS or SWL, but carries a higher risk of bleeding and is associated with a longer hospital stay; however, there is a high degree of heterogeneity among the included studies [353, 355]. Stones > 20 mm should be treated primarily by PCNL, because SWL often requires multiple treatments, and is associated with an increased risk of ureteral obstruction (colic or steinstrasse) with a need for adjunctive procedures (Figure 3.2) [358]. Retrograde renal surgery cannot be recommended as first-line treatment for stones > 20 mm in uncomplicated cases as SFRs decrease, and staged procedures will be required [359-361]. However, it may be a first-line option in patients where PCNL is not an option or contraindicated or in selected patients [362]. The combination of PCNL and RIRS may be a good alternative for the treatment of complex renal stones compared to standard PCNL; however, the level of the existing evidence is low [265].

3.4.10.4.2 Stones in the lower renal pole

The stone clearance rate after SWL seems to be lower for stones in the inferior calyx than for other intra-renal locations. Although the disintegration efficacy of SWL is not limited compared to other locations, the fragments often remain in the calyx and cause recurrent stone formation. The reported SFR of SWL for lower pole calculi is 25-95%. The preferential use of endoscopic procedures is supported by some current reports, even for stones < 1 cm [350, 352, 356, 358, 361, 363-370].

The following can impair successful stone treatment by SWL [371-377]:

- steep infundibular-pelvic angle;
- long calyx;
- long skin-to-stone distance;
- narrow infundibulum;
- shock wave-resistant stones (calcium oxalate monohydrate, brushite, or cystine).

Further anatomical parameters cannot yet be established. Supportive measures such as inversion, vibration or hydration may facilitate stone clearance (See 3.4.5 SWL) [174, 378, 379]. If there are negative predictors for SWL, PCNL and RIRS might be reasonable alternatives, even for smaller calculi [363]. Retrograde renal surgery seems to have comparable efficacy to SWL [350, 356, 358, 380]. Clinical experience has suggested a higher SFR of RIRS compared to SWL but at the expense of greater invasiveness. Depending on operator skills, stones up to 3 cm can be treated by RIRS [362, 381]. However, staged procedures are frequently required. Although mini-PCNL has the highest success rate for the treatment of lower pole stones up to 2 cm, it comes at the expense of a higher complication rate and longer hospital stay [355].

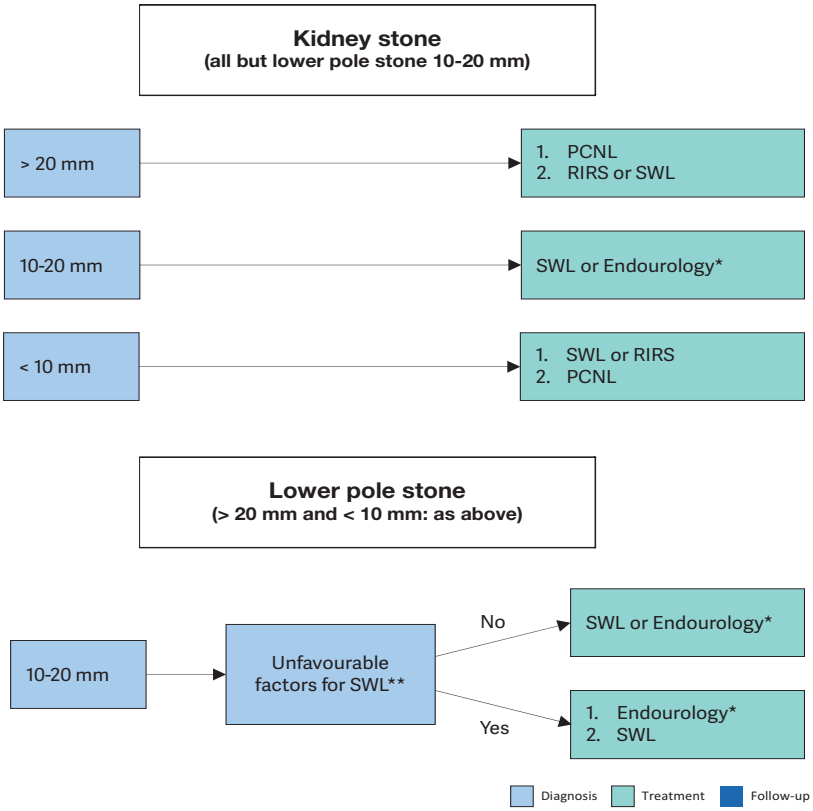
In complex stone cases, open or laparoscopic approaches are possible alternatives although they are infrequently used.

3.4.10.5 Summary of evidence and recommendations for the management of renal stones

Summary of evidence	LE
It is still debatable whether renal stones should be treated, or whether annual follow-up is sufficient for asymptomatic calyceal stones that have remained stable for six months.	4
Although the question of whether asymptomatic calyceal stones should be treated is still unanswered, stone growth, *de novo* obstruction, associated infection, and acute and/or chronic pain are indications for treatment.	3
Percutaneous nephrolithotomy is indicated in renal stones > 2 cm as primary option.	1a

Recommendations	Strength rating
Offer active treatment for renal stones in case of stone growth, *de novo* obstruction, associated infection, and acute and/or chronic pain.	Weak
Evaluate stone composition before deciding on the method of removal, based on patient history, former stone analysis of the patient or Hounsfield unit (HU) on unenhanced computed tomography.	Strong
Perform percutaneous nephrolithotomy (PCNL) as first-line treatment of larger stones > 2 cm.	Strong
Treat larger stones (> 2 cm) with flexible ureteroscopy or shock wave lithotripsy (SWL), in cases where PCNL is not an option. However, in such instances there is a higher risk that a follow-up procedure and placement of a ureteral stent may be needed.	Strong
Perform PCNL or retrograde intrarenal surgery for the lower pole, even for stones > 1 cm, as the efficacy of SWL is limited (depending on favourable and unfavourable factors for SWL).	Strong
Perform PCNL or retrograde intrarenal surgery for the lower pole, even for stones > 1 cm, as the efficacy of SWL is limited (depending on favourable and unfavourable factors for SWL).	Strong

Figure 3.2: Treatment algorithm for renal stones (if/when active treatment is indicated)



**The term 'Endourology' encompasses all PCNL and URS interventions.*
PCNL = percutaneous nephrolithotomy; RIRS = retrograde intrarenal surgery; SWL = shock wave lithotripsy; URS = ureteroscopy

3.4.11 *Laparoscopy and open surgery*

Advances in SWL and endourological surgery (URS and PCNL) have significantly decreased the indications for open or laparoscopic stone surgery [382-387]. There is a consensus that most complex stones, including partial and complete staghorn stones, should be approached primarily with PCNL. Additionally, a combined approach with PCNL and RIRS may also be an appropriate alternative. However, if 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 [388-392].

Few studies have reported laparoscopic stone removal. These procedures are usually reserved for special cases. When expertise is available, laparoscopic ureterolithotomy can be performed for large proximal ureteral stones as an alternative to URS or SWL [393, 394]. These more invasive procedures have yielded high SFRs and lower auxiliary procedure rates [196, 205, 389]. A systematic review showed no difference in the post-operative phase for stented or unstented laparoscopic ureterolithotomy [389].

Laparoscopic pyelolithotomy could be offered for solitary stones > 2 cm located in the renal pelvis as an alternative to PCNL [390]. In addition, in selected cases with an extrarenal and dilated pelvis, RLP can be considered as an alternative management of staghorn calculi [395].

A few studies with limited numbers of patients have reported using robotic surgery in the treatment of urinary stones [391]. Open surgery should be considered as the last treatment option after all other possibilities have been explored.

Studies on laparoscopy should be interpreted with caution due to their low design and quality of evidence.

3.4.11.1 *Recommendation for laparoscopy and open surgery*

Recommendation	Strength rating
Offer laparoscopic or open surgical stone removal in rare cases in which shock wave lithotripsy, retrograde or antegrade ureteroscopy and percutaneous nephrolithotomy fail, or are unlikely to be successful.	Strong

3.4.12 *Steinstrasse*

Steinstrasse is an accumulation of stone fragments or stone gravel in the ureter and may interfere with the passage of urine [396]. Steinstrasse occurs in 4% of cases of SWL [175, 183], and the major factor in the development of steinstrasse formation is stone size [397].

A major problem of steinstrasse is ureteral obstruction, which may be silent in up to 23% of cases. A MA including eight RCTs (n = 876) suggested a benefit of stenting before SWL in terms of steinstrasse formation but did not result in a benefit on SFRs or less auxiliary treatments [136]. When steinstrasse is asymptomatic, conservative treatment is an initial option. Medical expulsion therapy increases stone expulsion and reduces the need for endoscopic intervention [398, 399]. Ureteroscopy and SWL are effective in the treatment of steinstrasse [185, 400]. In the event of UTI or fever, the urinary system should be decompressed, preferably by percutaneous nephrostomy [113, 401].

3.4.12.1 *Summary of evidence and recommendations for steinstrasse*

Summary of evidence	LE
Medical expulsion therapy increases the stone expulsion rate of steinstrasse.	1b
Ureteroscopy is effective for the treatment of steinstrasse.	3
Only low-level evidence is available, supporting SWL or URS for the treatment of steinstrasse.	4

Recommendations	Strength rating
Treat steinstrasse associated with urinary tract infection (UTI)/fever preferably with percutaneous nephrostomy.	Weak
Treat steinstrasse when large stone fragments are present with shock wave lithotripsy or ureteroscopy (in absence of signs of UTI).	Weak

*3.4.13 **Management of patients with residual stones***

Following initial treatment with SWL, URS or PCNL, residual fragments may remain and require additional intervention [347, 402-405]. Most of these studies indicate that initial imaging is performed on the first day or the first week after treatment. However, false positive results from dust or residual fragments, that will pass spontaneously without causing any stone-related event, might lead to over-treatment. Therefore, imaging at four weeks seems most appropriate [406-408]. Compared to US, KUB and IVU, NCCT scan has a higher sensitivity to detect small residual fragments after definitive treatment of ureteral or kidney stones [409, 410].

A SR/MA examining residual fragments following any treatment has demonstrated that around a third of patients with either dust or fragments </= 4 mm experience disease progression and re-intervention within three years, whilst a third have spontaneous passage within two years regardless of imaging modality follow-up. For fragments > 4 mm, there are fewer studies, but these suggest low spontaneous passage rates and high intervention rates [411].

Although NCCT has the highest sensitivity to detect residual fragments, this must be balanced to the exposure to ionising radiation when compared with KUB and US. Recurrence risk in patients with residual fragments after treatment of infection stones is higher than for other stones [412].

3.4.13.1 Recommendation for management of patients with residual stones

Recommendation	Strength rating
Treat residual fragments > 4 mm.	Weak

*3.4.14 **Management of specific patient groups***

3.4.14.1 Management of urinary stones and related problems during pregnancy

Clinical management of a pregnant patient with urolithiasis is complex and demands close collaboration between the patient, radiologist, obstetrician, and urologist [64]. For diagnostic imaging see Section 3.3.1. Patients with urolithiasis may be at increased risk of developing adverse maternal or neonatal outcomes [413].

Conservative approaches for symptomatic hydronephrosis as well as for ureteric calculi are the preferred initial management option in pregnant patients [414, 415].
If spontaneous passage does not occur, or if complications develop (e.g., intractable symptoms, severe hydronephrosis, spontaneous renal fornix rupture [416] or induction of premature labour), placement of a ureteral stent or a percutaneous nephrostomy tube is necessary as it is more effective than conservative treatment for symptom relief [417-419].

In the treatment of renal stones during pregnancy, when a stent is necessary, PCNL versus ureteral stent placement does not confer a significant difference in rates of adverse pregnancy events. However, ureteral stent placement was associated with a lower incidence of hospital admissions, emergency department visits, exchange procedures, and new UTIs or pyelonephritis [420].

Ureteroscopy has become a reasonable alternative in these situations [408, 421]. When compared to temporary ureteral JJ stenting until after delivery, ureteroscopy resulted in fewer needs for stent exchanges, less irritative LUTS and better patient satisfaction [422, 423].

Non-urgent ureteroscopy in pregnant women is best performed during the second trimester, by an experienced urologist. Counselling of the patient should include access to neonatal and obstetric services [72].

Although feasible, percutaneous removal of renal stones during pregnancy remains an individual decision and should be performed only in experienced centres [424]. Pregnancy remains an absolute contraindication for SWL.

3.4.14.1.1 Summary of evidence and recommendation for the management of urinary stones and related problems during pregnancy

Summary of evidence	LE
Stent insertion seems to be more effective than conservative treatment in the management of symptomatic moderate-to-severe hydronephrosis during pregnancy.	1a
Ureteroscopy is a reasonable alternative to avoid long-term stenting/drainage.	1b
There is a higher tendency for stent encrustation during pregnancy.	3

Recommendation	Strength rating
Treat all uncomplicated cases of urolithiasis in pregnancy conservatively (except when there are clinical indications for intervention).	Strong

3.4.14.2 Management of stones in patients with urinary diversion

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 [425, 426]. Metabolic factors (hypercalciuria, hyperoxaluria and hypocitraturia), infection with urease-producing bacteria, foreign bodies, mucus secretion, and urinary stasis are responsible for stone formation [427] (section 3.1.3). One study has shown that the risk for recurrent upper tract stones in patients with urinary diversion subjected to PCNL was 63% at five years [428].

Management

Smaller upper-tract stones can be treated effectively with SWL [429, 430]. In most cases, endourological techniques are necessary to achieve stone-free status [431]. In individuals with long, tortuous conduits or with invisible ureter orifices, a retrograde endoscopic approach might be difficult or impossible [432].

For stones in the conduit, a trans-stomal approach can be used to remove all stone material (along with the foreign body) using standard techniques, including intracorporeal lithotripsy and flexible endoscopes. Trans-stomal manipulations in continent urinary diversion must be performed carefully to avoid disturbance of the continence mechanism [433].

Before considering any percutaneous approach in these cases, CT should be undertaken to assess the presence of overlying bowel, which could make this approach unsafe [434], and if present, a surgical approach should be considered.

Prevention

Recurrence risk is high in patients with urinary diversion [428]. Metabolic evaluation and close follow-up are necessary to obtain the risk parameters for effective long-term prevention. Preventive measures include medical management of metabolic abnormalities, appropriate therapy of urinary infections, and hyper-diuresis or regular irrigation of continent reservoirs [435].

3.4.14.2.1 Summary of evidence and recommendation for the management of stones in patients with urinary diversion

Summary of evidence	LE
The choice of access depends on the feasibility of orifice identification in the conduit or bowel reservoir. Whenever a retrograde approach is impossible, percutaneous access with antegrade ureteroscopy is the alternative.	4

Recommendation	Strength rating
Perform percutaneous lithotomy to remove large renal stones in patients with urinary diversion, as well as for ureteral stones that cannot be accessed via a retrograde approach, or that are not amenable to shock wave lithotripsy.	Strong

3.4.14.3 Management of stones in patients with neurogenic bladder

Aetiology, clinical presentation, and diagnosis

Patients with neurogenic bladder develop urinary calculi because of additional risk factors such as bacteriuria, hydronephrosis, VUR, renal scarring and lower urinary tract reconstruction [436, 437]. The most common causes are urinary stasis and infection (Section 3.1.3). Indwelling catheters and surgical interposition of bowel segments for treatment of bladder dysfunction both facilitate UTI. Although calculi can form at any level of the urinary tract, they occur more frequently in the bladder; especially if bladder augmentation has been performed [438, 439].

Diagnosis of stones may be difficult and delayed in the absence of clinical symptoms due to sensory impairment and vesicourethral dysfunction. Difficulties in self-catheterisation should lead to suspicion of bladder calculi. Imaging studies are needed (US, CT) to confirm the clinical diagnosis prior to surgical intervention.

Management

Management of calculi in patients with neurogenic bladder is similar to that described in Section 3.3. 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 [440]. The risk of stone formation after augmentation cystoplasty in immobile patients with sensory impairment can be significantly reduced by irrigation protocols [435].

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.

3.4.14.3.1 Summary of evidence and recommendation for the management of stones in patients with neurogenic bladder

Summary of evidence	**LE**
Patients undergoing urinary diversion and/or suffering from neurogenic bladder dysfunction are at risk for recurrent stone formation.	3

3.4.14.4 Management of stones in patients with transplanted kidneys

Stones in transplanted kidneys can either be transplanted or present *de novo* allograft stones. Usually, they are detected by routine US examination, followed by NCCT in cases of unclear diagnosis [441].

Aetiology

Transplant patients depend on their solitary kidneys for renal function. Impairment causing urinary stasis/obstruction, therefore, requires immediate intervention or drainage of the transplanted kidney. Stones in kidney allografts have an incidence of 2% [441]. Risk factors for *de novo* stone formation in these patients are multi-fold:

- Immunosuppression increases the infection risk, resulting in recurrent UTIs.
- Hyper-filtration, excessively alkaline urine, renal tubular acidosis (RTA), and increased serum calcium caused by persistent tertiary hyperparathyroidism [442] are biochemical risk factors.

Management

Selecting the appropriate technique for stone removal in a transplanted kidney is difficult, although management principles are like those applied in other single renal units [443-445]. Additional factors such as transplant function, coagulative status, and anatomical alterations due to the iliac 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 URS a valid treatment option for transplant calculi; however, one must be aware of potential injury to adjacent organs [444, 446, 447]. Retrograde access to transplanted kidneys can be difficult due to the anterior location of the ureteral anastomosis, and ureteral tortuosity [448-450]. Treatment of donor stones may be needed pre-transplant and increases the pool available for renal transplants. Post-transplant stone disease may also need treatment to maintain the allograft function. A systematic review evaluating the outcomes of pre- vs. post-transplant URS demonstrated a 100% SFR with an overall 7.5% complication rate, compared to a SFR of 60-100% with an overall complication rate of 12.9% for post-transplant URS; most complications were Clavien 1 [451]. A SR shows that SWL is also a safe and effective option for *de novo* stones after transplantation, with an overall SFR of 81% and a complication rate of 17.2% [452].

3.4.14.4.1 Summary of evidence and recommendation for the management of stones in patients with transplanted kidneys

Summary of evidence	LE
Conservative treatment for small asymptomatic stones is only possible under close surveillance and in absolutely compliant patients.	3
Shock wave lithotripsy for small calyceal stones is an option with minimal risk of complication, but localisation of the stone can be challenging.	3

Recommendation	Strength rating
Offer patients with transplanted kidneys any of the contemporary management options, including shock wave lithotripsy, flexible ureteroscopy and percutaneous nephrolithotomy.	Strong

3.4.14.5 Special problems in stone removal

Table 3.11: Special problems in stone removal [453]

Calyceal diverticulum stones	• SWL, PCNL [454] (if possible) or RIRS [454, 455]. • Can also be removed using laparoscopic retroperitoneal surgery [456, 457]. • Patients may become asymptomatic due to stone disintegration (SWL), whilst well-disintegrated stone material remains in the original position due to narrow calyceal neck.
Horseshoe kidneys	• Can be treated in line with the options described above [458-460]. • Passage of fragments after SWL might be poor. • Acceptable SFRs (up to 76%) with low major complication rates (2.4%) can be achieved with flexible ureteroscopy [458-460].
Stones in pelvic kidneys	• SWL, RIRS, PCNL or laparoscopic surgery [461].
Stones formed in a continent reservoir	• Each stone must be considered and treated individually.
Patients with obstruction of the UPJ	• When outflow abnormality requires correction, stones can be removed by PCNL together with percutaneous endopyelotomy or open/laparoscopic reconstructive surgery. • URS together with endopyelotomy with Ho:YAG laser [462].

3.4.15 ***Management of stones in children***

The true incidence of nephrolithiasis in children remains unclear due to the global lack of large epidemiological studies. Data derived from nationwide epidemiological studies, studies performed in different counties worldwide [463] and large-scale databases [464, 465] indicate that the incidence and prevalence of paediatric urinary stone disease have increased over the last few decades. Although boys are most commonly affected in the first decade of life [466] the greatest increase in incidence has been seen in older female adolescents [463].
Stone composition is similar in children as in adults, with a predominance of calcium oxalate stones. Compared to historical data, metabolic abnormalities responsible for stone formation are less commonly identified in children nowadays [467-469]. Hypocitraturia, low urine volume and hypercalciuria predominate [84, 467-469]. Age may affect the predominant metabolic abnormality with hypercalciuria and hypocitraturia being the most common disorder present in children < 10 and > 10 years old, respectively [469]. Genetic or systemic diseases (e.g., cystinuria or nephrocalcinosis) contributing to stone formation are relatively frequent in children accounting for less than 17% of the identifying causes [467, 470]. The role of diet remains unclear in children, although there is some evidence that children are drinking less water and taking greater daily amounts of sodium than is recommended [471-473].

For diagnostic procedures see Section 3.3.3.2, for acute decompression see Section 3.4.2. and for metabolic evaluation see Chapter 4.

3.4.15.1 Clinical presentation

Children with urinary stones can be asymptomatic or present with non-specific symptoms that necessitate a high index of suspicion for proper diagnosis. Symptoms are age-dependent with infants presenting with crying,

irritability and vomiting in 40% of cases [474] while in older children flank pain, micro or gross haematuria and recurrent UTIs are more common [475].

3.4.15.2 Conservative management

There is a lack of evidence on conservative management of paediatric stones with evidence for ureteric calculi coming from the placebo arms of medical expulsive trials, while evidence for renal stones comes from small cohort studies, either on primary stones [476, 477] or residual fragments remained after SWL, RIRS or PCNL [478]. Expectant management for single, asymptomatic lower-pole renal stones could be the initial approach with increased odds of stone passage, especially in patients with non-struvite, non-cystine stones < 7 mm, with no anatomic abnormalities [476]. Intervention may be needed for stones located elsewhere independently of their size [476-478].

3.4.15.3 Medical expulsive therapy in children

There are limited studies on MET as off-label expulsive therapy for children with ureteral stones up to 10 mm which show conflicting outcomes. Several systematic reviews and meta-analyses, including six RCTs and one conference abstract of an RCT, have been performed, all unanimously reporting that the use of alpha-blockers for distal ureteric stones increases the stone-free or stone expulsion rate [479-481]. The use of alpha-blockers also reduces the stone expulsion time and decreases pain episodes and analgesia demand with the disadvantage of more side-effects such as headache and nasal congestion [480, 481].

3.4.15.4 Extracorporeal shock wave lithotripsy

Shock wave lithotripsy is still the first-line treatment for most ureteral stones in children. However, it is less likely to be successful for stones > 10 mm in diameter, impacted stones, calcium oxalate monohydrate or cystine stones, or for stones in children with unfavourable anatomy and in whom localisation is difficult [482].

Studies on extracorporeal SWL in children suggest an overall SFR of 70-90%, retreatment rate of 4-50% and need for auxiliary procedures in 4-12.5% of cases [483-487]. A MA of fourteen studies reporting on 1,842 paediatric patients treated with SWL found significantly higher SFR for stones < 10 mm than for stones > 10 mm and higher retreatment rates as the stone size increased [482]. For best clinical practice see Section 3.4.5. A MA on slow SWL vs. rapid SWL for renal stones revealed very low-quality evidence about the effects of SWL on SFRs, serious adverse events or complications of treatment and secondary procedures for residual fragments [479]. Shock wave lithotripsy is well tolerated; however, good treatment outcomes are more likely to require the administration of general anaesthesia to children. With improvements in modern (second and third-generation) lithotripters, successful treatment using intravenous sedation, patient-controlled analgesia or no medication at all has been increasingly performed in a select population of older, co-operative children [488].

Based on the results of a MA which compared SWL to dissolution therapy for intra-renal stones, and SWL to ureteroscopy with holmium laser or pneumatic lithotripsy for renal and distal ureteric stones, no firm conclusions can be drawn about the effects of SWL on SFR, serious adverse events or complications of treatment and secondary procedures for residual fragments [479]. When SWL was compared to mini-percutaneous nephrolithotomy for lower pole renal stones 1-2 cm in size SWL resulted in lower SFRs (RR: 0.88, 95% CI: 0.80 - 0.97; moderate-quality evidence) and higher rates of secondary procedures (RR: 2.50, 95% CI: 1.01 - 6.20; low-quality evidence); however, SWL showed less severe adverse events (RR: 0.13, 95% CI: 0.02 - 0.98; low-quality evidence) [489].

3.4.15.5 Endourological procedures

Rigid/semi-rigid ureteroscopy

In recent years ureteroscopy is increasingly used in children with ureteral stones [490]. Ureteroscopy proved to be effective with SFR of 81-98% [491-493], retreatment rates of 6.3%-10% [494] and complication rates of 1.9-23% [491-493, 495]. Similar to adults, routine stenting is not necessary before URS. Pre-stenting may facilitate URS, increase SFR and decrease complication rates [496, 497].

Flexible ureteroscopy/retrograde intrarenal surgery

Retrograde intra-renal surgery with flexible ureteroscopes (FURS) has become an efficacious treatment modality for paediatric renal stones. Studies report SFRs of 76-100%, retreatment rates of 0-19% and complication rates of 0-28% [498-501]. Younger age, cystine composition [502], large stone diameter [501] and lack of pre-stenting predispose to FURS failure in children [496]. A large global study across eight centres shows an SFR of 75.5%; although complications were minor, they were higher in patients < 5 years of age [503].

Although high-level evidence is lacking to support a strong recommendation [479], FURS may be a particularly effective treatment option for lower calyceal stones in the presence of unfavourable factors for SWL [493, 499, 504].

For large and complex kidney stones RIRS has a significantly lower SFR compared to PCNL (71% vs. 95%), but is associated with less radiation exposure, lower complication rates, and a shorter hospital stay [505]. Similarly, retrospective data indicate that RIRS may achieve lower SFRs compared to micro percutaneous surgery in favour of shorter operative time, shorter fluoroscopy time, and less hospitalisation time [506, 507]. A published MA confirmed these results [508].

Percutaneous nephrolithotomy

Indications for PCNL in children are like those in adults and include renal stones > 2 cm, or smaller stones resistant to SWL and ureteroscopic treatment. Reported SFRs with paediatric PCNL are 71.4-95% after a single session [505-507, 509, 510] with an overall complication rate of 20% [511]. A high degree of hydronephrosis, increased number of tracts and operative time [512], and large tract size [510, 513-515] are associated with increased blood loss. Child age [514] and stone burden [510] predispose to the use of larger instruments during PCNL in children. The miniaturisation of equipment increases the opportunity to perform tubeless PCNL in appropriately selected children, which can reduce the length of hospital stay and post-operative pain [516, 517]. A systematic review on the role of mini-PCNL showed an initial and overall SFR of 87.9% and 97% respectively, with no conversions to standard PCNL, and a complication rate of 19%, with a mean transfusion rate of 3.3% [503].

Concerns have been raised regarding the possible adverse effects of PCNL on the renal parenchyma of the developing child. However, focal damage is only reported in 5% of cases [518]. Using pre- and post-PCNL dimercaptosuccinic acid (DMSA) scans, Cicekbilek *et al.* demonstrated that PCNL tracts between 12-24 Charrière in size did not cause significant harm to paediatric kidneys [509].

3.4.15.6 Open and laparoscopic/robot-assisted stone surgery

With the advances in SWL, PCNL and RIRS, very few cases of paediatric urolithiasis require open surgery. Data extracted from the National Inpatient Sample (NIS) databases for 2001-2014 showed that in the USA incisional procedures (mainly nephrolithotomy, pyelolithotomy and ureterotomy) were performed in 2.6% of hospitalised patients (52% aged 15-17 years) who required surgical intervention for urinary stones [519]. Laparoscopy for the management of paediatric renal and ureteric stones is a safe and effective procedure when specific indications are followed. Stone-free rates of 100% were reported when laparoscopic pyelolithotomy was applied for a ≥ 1 cm single stone located in an extra-renal pelvis [520], or when laparoscopic ureterolithotomy was applied to impacted ureteric stones ≥ 1.5 cm, or to ureteric stones that were refractory to SWL or URS [521]. There are extremely limited data available on the efficacy and complications of robot-assisted laparoscopic management of paediatric urolithiasis [522].

3.4.15.7 Special considerations on recurrence prevention

All paediatric stone formers need metabolic evaluation and recurrence prevention with respect to the detected stone type. Children are in the high-risk group for stone recurrence (See Chapter 4).

3.4.15.8 Summary of evidence and recommendations for the management of stones in children

Summary of evidence	**LE**
In children, MET could increase the rate of stone expulsion, reduce the stone expulsion time, and decrease pain episodes/analgesia demand, but it has a higher incidence of side effects.	1b
In children, the indications for SWL, URS and PCNL are similar to those in adults.	1b
Children with renal stones of a diameter up to 20 mm (~300 mm^2) are ideal candidates for SWL.	1b
Ureteroscopy has become the treatment of choice for larger distal ureteral stones in children.	1a
In children, the indications for PCNL are similar to those in adults.	1a
Mini-PCNL is safe and effective in children.	1b

Recommendations	**Strength rating**
Offer children with single ureteral stones less than 10 mm shock wave lithotripsy (SWL) if localisation is possible or ureteroscopy as first-line option.	Strong
Ureteroscopy is a feasible alternative for ureteral stones not amenable to SWL.	Strong
Offer children with renal stones with a diameter of up to 20 mm (~300 mm^2) SWL.	Strong
Offer children with renal pelvic or calyceal stones with a diameter > 20 mm (~300 mm^2) percutaneous nephrolithotomy.	Strong
Retrograde renal surgery is a feasible alternative for renal stones smaller than 20 mm in all locations.	Weak

3.5 Radiation exposure and protection during endourology

The diagnosis and treatment of nephrolithiasis are associated with high levels of ionising radiation exposure to patients [523, 524]. Currently, there are no studies estimating the lifetime radiation exposure of stone formers or the subsequent risk of malignancy development. The radiation exposure of endourologists has been extensively studied. Still, there are no studies assessing the risk of radiation-induced malignancies in urologists or operating theatre staff members [525-527].

Current evidence from atomic bomb patients [528, 529], retrospective epidemiological data on medical exposure [530, 531], and modelling studies [532, 533] suggest an age and dose-dependent risk of secondary malignancy from ionising radiation.

The International Commission on Radiological Protection (ICRP) recommends a maximum annual occupational exposure of 50mSv [534]. However, the risk of radiation-induced malignancy follows a stochastic model having no known safe threshold of exposure. Taking this into consideration as well as the length of a urologist's career the upper limit of 50mSv is still highly concerning.

Table 3.12 shows the EAU Urolithiasis guidelines panel recommended protection methods to reduce radiation exposure to patients, surgical, anaesthesiologic, and nursing staff.

Table 3.12 Radiation protection measures

Limit studies or intervention involving radiation exposure to those that are strictly medically necessary.
Implement a patient electronic record of medical imaging.
Make use of imaging studies with lower radiation doses (US, KUB, digital tomosynthesis, low-dose and ultra-low dose CT scan).
Create and follow a precise radiation exposure protection protocol in your department.
Act in accordance with the as low as reasonably achievable (ALARA) principle.
Measure and report fluoroscopy time to the operative surgeon (use dosimeters and perform monthly calculations).
Technical measures to reduce radiation exposure include: • Reducing fluoroscopy time; • Limiting time adjacent to patient; • Using low-dose radiation; Irradiating only to observe motion; • Intra-operative use of pulsed fluoroscopy; • Reduced fluoroscopy pulse rate; • Collimated fields; • Avoid digital image acquisition and rely on last image hold and instant replay technology.
Use radiation protection instruments (chest, pelvic and thyroid shields, lead or lead-free gloves, protective glasses, lead protection under the operating table between the x-ray source and the surgeon).
The radiation protection instruments must be cared for appropriately as any damage decreases effectiveness and increases exposure risk. They should be monitored and measured regularly to ensure integrity.
Proper surgeon and operating room setup should be observed (follow the inverse square law, use the x-ray source underneath the patient's body, decrease the x-ray source to patient distance, reduce magnification, avoid field overlap by not turning the C-arm in extreme angles, operate in the standing rather than the seated position).

The availability of fluoroscopy is mandatory for endourological procedures. There is an increasing interest in fluoroless and fluoroscopy-free operations in urology. Several RCTs have been published showing a good outcome in means of stone-free and complication rates [166, 270, 535-537]. These trials have been limited to non-complex cases and they were not sufficiently powered to show the non-inferiority of fluoroscopy in PCNL [270, 525] or the superiority of ultrasound in URS [213, 214].

4. METABOLIC EVALUATION AND RECURRENCE PREVENTION

4.1 General metabolic considerations for patient work-up

4.1.1 *Evaluation of patient risk*

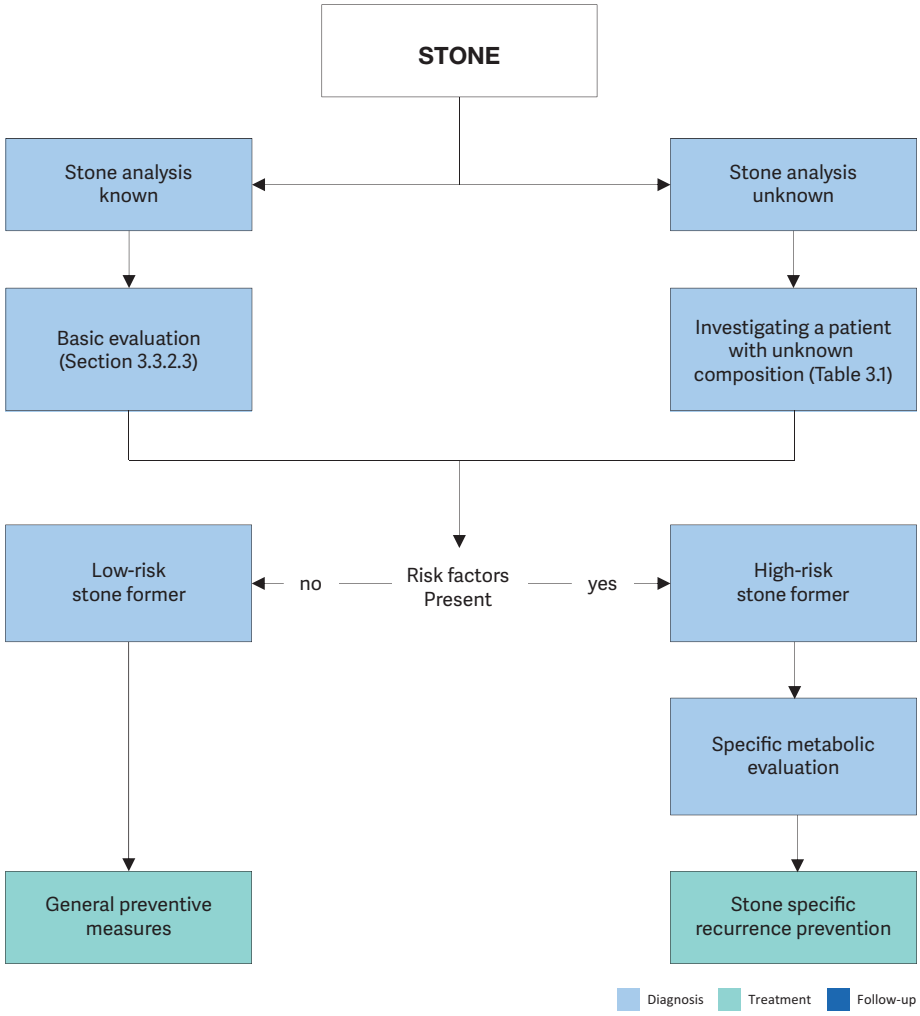
After stone passage, every patient should be assigned to a low- or high-risk group **(Table 3.3)** for stone formation (Figure 4.1).

Reliable stone analysis by infrared spectroscopy or X-ray diffraction and basic metabolic evaluation is mandatory for all stone formers.

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.

Figure 4.1: Assignment of patients to low- or high-risk groups for stone formation



4.1.2 Urine sampling

Specific metabolic evaluation requires the collection of two consecutive 24-hour urine samples [63, 538, 539]. The collecting bottles should be prepared with 1 g thymol per liter or stored at < 8°C during collection to reduce bacterial proliferation [63]. 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, but this prevents the correct determination of pH [63]. The collecting method should be chosen in close cooperation with the laboratory. A pH < 5.5 in a 24-hour urine indicates hyper acidic urine (acidic arrest) [540-542]. In the course of alkalinising therapy for cystinuria and uric acid stones, urine pH should be assessed during the collection of freshly voided urine at different times throughout the day using sensitive pH dipsticks or a pH-meter [23, 63, 543]. A consensus statement stated that RTA is suspected if 24-hour urine pH is > 6.2 and fasting second-morning spot urine pH is > 5.8 [544, 545].

Spot urine samples are an alternative sampling method, particularly when 24-hour urine collection is difficult, for example, in non-toilet-trained children [546]. Spot urine studies normally link the excretion rates to the creatinine [547], but these are of limited use because the results may vary with collection time and patients' sex, body weight, and age.

4.1.3 Timing of specific metabolic work-up

For the initial specific metabolic work-up, the patient should stay on a self-determined diet under normal daily conditions and should ideally be stone-free for at least twenty days [548]. Follow-up studies are necessary for patients taking medication for recurrence prevention [549]. The first follow-up 24-hour urine measurement is suggested eight to twelve weeks after starting pharmacological prevention of stone recurrence. This enables diet and/or drug dosage to be adjusted if urinary risk factors have not normalised, with further 24-hour urine measurements, if necessary. Once urinary parameters have been normalised, it is sufficient to perform a 24-hour urine evaluation every twelve months. On this issue, the Panel realises that there is only very limited published evidence.

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 [23, 549]

Blood parameter	Reference range	
Creatinine	50-100 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	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 the urine [550-553]. However, clinical validation of these risk indices for recurrence prediction or therapy improvement is ongoing.

Table 4.2: Laboratory values for urinary parameters in adults

Urinary Parameters	Reference ranges and limits for medical attention
pH	Consistently fasting morning spot urine pH > 5.8 and > 6.2 in 24-hr collection (suspicious of renal tubular acidosis) [544, 545]
	Consistently > 7.0 (suspicious of infection)
	Consistently < 5.5 in morning urine and in 24-hr collection (suspicious of acidic arrest) [540, 554]
Specific weight	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 (females), 5 mmol/day (males)
Citrate	< male < 1.7 mmol/day, female < 1.9 mmol/day
Magnesium	< 3.0 mmol/day
Inorganic phosphate	> 35 mmol/day
Ammonium	> 50 mmol/day
Cystine	> 0.8 mmol/day

Table 4.3: Normal values for spot urine samples: creatinine ratios (solute/creatinine) in children [555]

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/mg**
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		
> 2 years	< 0.56 mg/dL (33 µmol/L) per GFR (ratio x plasma creatinine)	

** There is low-level evidence regarding the importance of magnesium.*

Table 4.4: Solute excretion in 24-hour urine samples in children [556, 557]*

Calcium/24	Citrate/24 hour		Cystine/24 hour		Oxalate/24 hour		Urate/24 hour	
All age groups	Boys	Girls	< 10 years	> 10 years	All age groups	< 1 year	1-5 years	> 5 years
< 0.1 mmol/kg/ 24 h	> 1.9 mmol/ 1.73 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 is the normalisation of dietary habits and lifestyle risks. Stone formers at high risk need specific prophylaxis for recurrence, which is usually pharmacological treatment based on stone analysis and urinary risk profile.

Table 4.5: General Preventive Measures

Fluid intake (drinking advice)	Fluid amount: 2.5-3.0 L/day
	Water is the preferred fluid
	Diuresis: 2.0-2.5 L/day
	Specific weight of urine: < 1,010 g/day
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 advise to normalise general risk factors	Retain a normal BMI level
	Adequate physical activity
	Balancing of excessive fluid loss
	Reduce the intake of alcohol containing fluids
	Reduce the intake of sodas and calorie-containing fluids

Caution: Protein requirements are 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 [556-560]. The beneficial effect of fruit juices is mainly determined by the presence of citrate or bicarbonate [561]. Citrus fruit juices seem to protect against stone disease either by increasing urinary citrate levels or by having an alkalinising effect on it [562]. However, if potassium is present, both pH and citrate are increased [563, 564]. One large moderate-quality RCT randomly assigned men with more than one past renal stone of any type and soft drink consumption of at least 160 mL/day to reduced soft drink intake or no treatment. Although the intervention significantly reduced the risk for symptomatic recurrent stones (RR: 0.83; CI: 0.71-0.98), the level of evidence for this outcome is low because the results were from only one trial [565]. An analysis of 3 Channing's cohorts (194,095 participants) over a median follow-up of more than eight years has shown that consumption of sugar-sweetened soda and punch is associated with a higher risk of stone formation, whereas consumption of coffee, tea, beer, wine, and orange juice is associated with a lower risk [566], whereas consumption of tea and coffee does not seem to increase the risk of stones disease [567]. However, the intake of fluids should be considered within a holistic approach to health. Some of them contain calories or alcohol that may be detrimental to health. Therefore, water should be the preferred fluid.

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 [557, 568, 569]. Sufficient calcium intake is needed especially in vegetarian and vegan diets [570].

Fruit, vegetables and fibre: Fruit and vegetable intake should be encouraged because of the beneficial effects of fiber, although the role of the latter in preventing stone recurrences is debatable [571-574]. The alkaline content of a vegetarian diet also increases urinary pH. In addition, fruits and vegetables have a high-water content and can significantly contribute to fluid intake.

Oxalate: Excessive intake of oxalate-rich products should be limited or avoided to prevent high oxalate load [575], 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 [576]. However, it seems wise to advise calcium oxalate stone formers to avoid excessive intake.

Animal protein: Animal protein should not be consumed in excess [577, 578] 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: Calcium should not be restricted, unless there are strong reasons for doing so, due to the inverse relationship between dietary calcium and stone formation [572, 579]. The daily requirement for calcium is 1,000 to 1,200 mg [23]. Calcium supplements are not recommended except in enteric hyperoxaluria when additional calcium should be taken with meals to bind intestinal oxalate [557, 575, 577, 580]. Older adults who do not have a history of renal stones but who take calcium supplements should ensure adequate fluid intake since it may prevent increases in urine calcium concentration, and thereby reduce or eliminate any increased risk of renal stones formation associated with calcium supplement use [581].

Sodium: Daily sodium (NaCl) intake should not exceed 4-5g [23]. High intake adversely affects urine composition:

- Calcium excretion is increased by reduced tubular re-absorption;
- 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 [577, 578]. A positive correlation between sodium consumption and the risk of first-time stone formation has been confirmed only in women [579]. 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 [582, 583] and uric acid stones. Intake should not exceed 500 mg/day [23].

*4.2.2 **Lifestyle***

Lifestyle factors may influence the risk of stone formation, for example, those causing obesity [584], diabetes mellitus [585], and metabolic syndrome [586].

*4.2.3 **Summary of evidence and recommendation for recurrence prevention***

Summary of evidence	**LE**
Increasing water intake reduces the risk of stone recurrence.	1a

Recommendation	**Strength rating**
Advise patients that a generous intake of fluids, preferably water, is to be maintained, allowing for a 24-hour urine volume > 2.5 L.	Strong

4.3 Stone-specific metabolic evaluation and pharmacological recurrence prevention

4.3.1 Introduction

Pharmacological treatment is necessary in patients at high risk for stone formation or for associated systemic conditions. 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	3.25-9.75 g/d (10-30 mmol/d) Children: 0.1-0.15 g/kg/d	Daily dose for alkalinisation depends on urine pH.	Calcium oxalate Uric acid Cystine	[587-592]
Allopurinol	Hyperuricosuria Hyperuricaemia	100-300 mg/d Children: 1-3 mg/kg/d	100 mg in isolated hyperuricosuria. Renal insufficiency demands dose correction. Contraindicated in acute gout pregnancy, and breastfeeding. Allergies from trivial to very severe forms, xanthine stone formation.	Calcium oxalate Uric acid Ammonium urate 2,8-Dihydroxyadenine	[557, 593-596]
Calcium	Enteric hyperoxaluria	Up to 2,000 mg/d depending on oxalate excretion	Intake 30 min before meals.	Calcium oxalate	[577, 579, 580, 597]
Captopril	Cystinuria Active decrease of urinary cystine levels	75-150 mg	Second-line option in case of significant side effects of tiopronin.	Cystine	[598, 599]
Febuxostat	Hyperuricosuria Hyperuricaemia	80-120 mg/d	Contraindicated in acute gout, pregnancy and breastfeeding. Xanthine stone formation.	Calcium oxalate Uric acid	[600, 601]
L-Methionine	Acidification	600-1,500 mg/d	Hypercalciuria, bone demineralisation, systemic acidosis. No long-term therapy.	Infection stones Ammonium urate Calcium phosphate	[587, 602]
Magnesium	Isolated Hypomagnesuria Enteric hyperoxaluria	200-400 mg/d Children: 6 mg/kg/d	Renal insufficiency demands dose correction. Diarrhoea, chronic alkali losses, hypocitraturia.	Calcium oxalate	[603, 604] (Low level of evidence)
Sodium bicarbonate	Alkalinisation Hypocitraturia	4.5 g/d	Daily dose for alkalinisation depends on urine pH	Calcium oxalate Uric acid, Cystine	[605]

Pyridoxine	Primary hyperoxaluria	Initial dose 5 mg/kg/d Max. 20 mg/kg/d	Sensory peripheral neuropathy	Calcium oxalate	[606]
Thiazide (Hydro-chlorothiazide*)	Hypercalciuria	25-50 mg/d Children: 0.5-1 mg/kg/d	Risk for hypotension diabetes, hyperuricaemia, hypokalaemia, hypocitraturia.	Calcium oxalate Calcium phosphate	[583, 587-596, 598-616]
Tiopronin	Cystinuria Increase in solubility of levels	Initial dose 800 mg/d Avg. 2,000 mg/d** Children: Initial dose in patients > 20kg is 15 mg/kg/day. Avoid dosages > 50mg/kg/day	Risk for proteinuria.	Cystine	[617-620]

** Patients on hydrochlorothiazide should be advised to get their skin checked on a regular basis as they have a higher risk of developing a non-melanoma skin cancer (NMSC) and some forms of melanoma. In patients with a history of skin cancer, the indication for treatment with hydrochlorothiazide should be thoroughly reviewed [621-623].*

*** No information is available on maximum dose and patients may be initiated on a very low dose if they have previously had reactions to tiopronin or penicillamine. For all patients, dosage should be titrated according to the frequency of stone episodes, side effects, and renal function under expert supervision with close monitoring.*

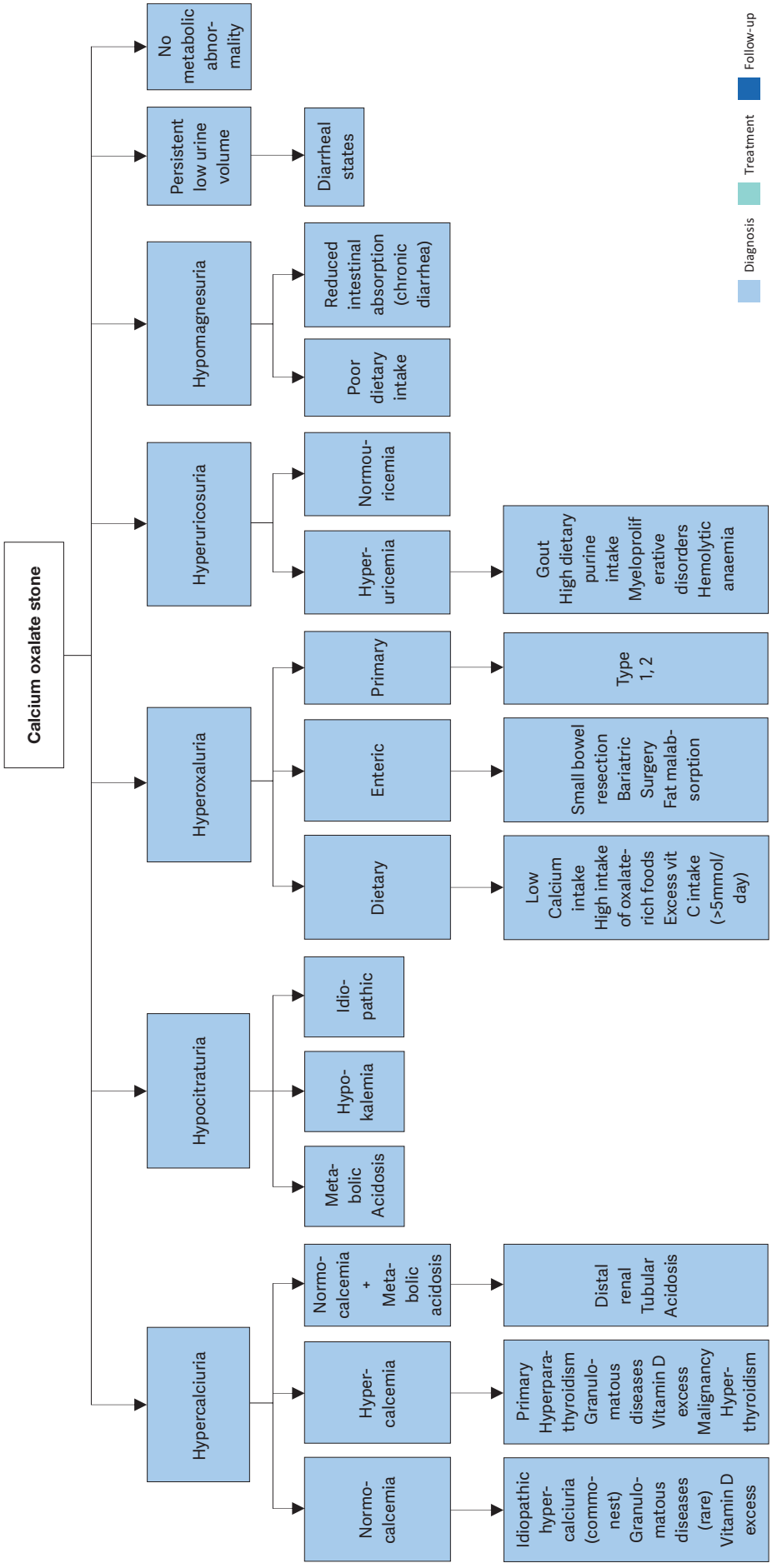
4.4 Calcium oxalate stones

The criteria for identification of calcium oxalate stone formers with a high risk of recurrences and comorbidities are listed in section 3.1.3.

*4.4.1 **Diagnosis***

Blood analysis requires measurement of creatinine, sodium, potassium, chloride, ionised calcium (or total calcium + albumin), phosphate, uric acid; and, in the case of increased calcium levels, parathyroid hormone (PTH) and vitamin D. Urinalysis requires measurement of urine volume, urine pH, specific weight, calcium, oxalate, uric acid, citrate, sodium, and magnesium. Figure 4.2 summarises the diagnostic steps for calcium oxalate stones.

Figure 4.2 Diagnostic algorithm for Calcium Oxalate stones

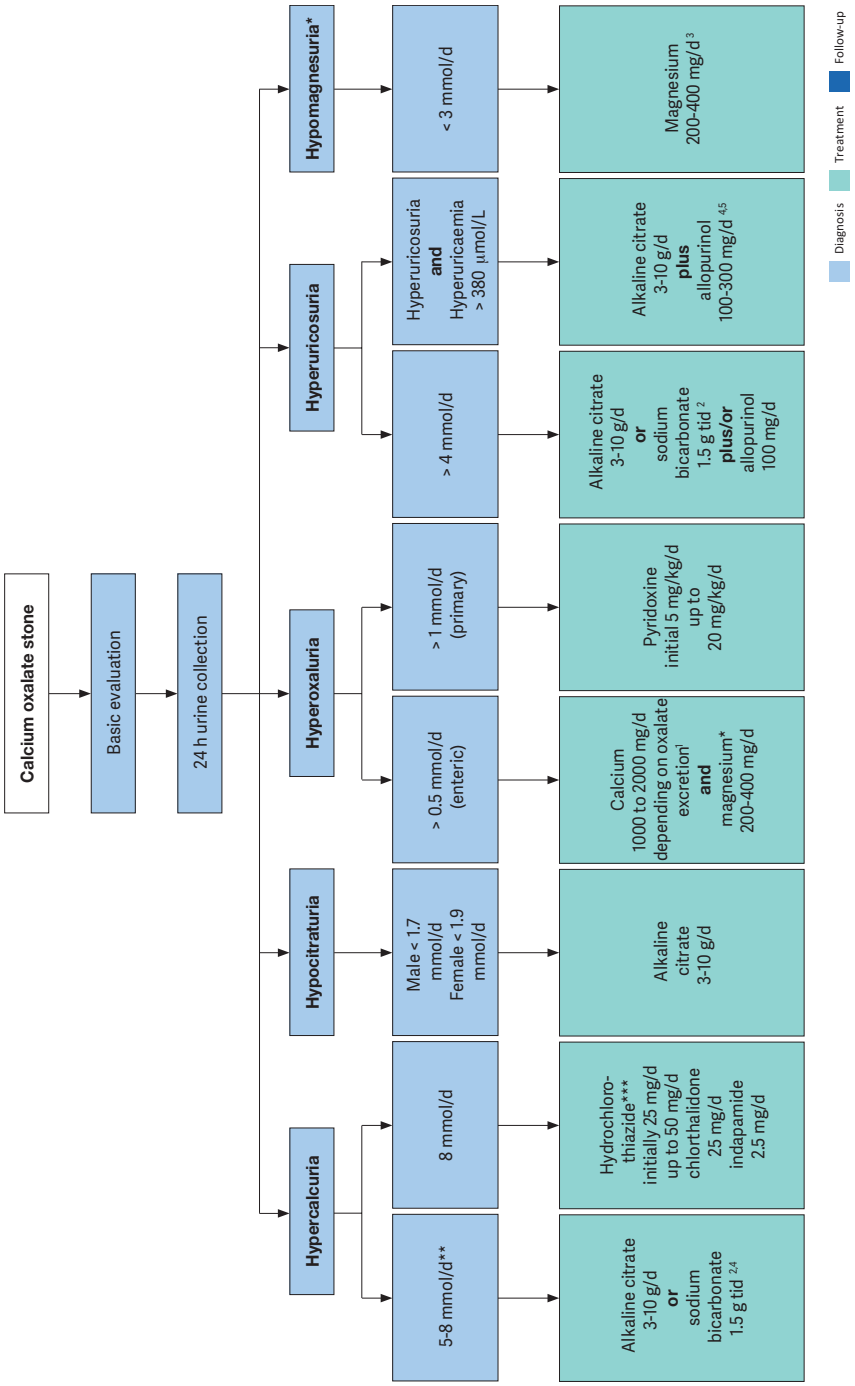


*4.4.2 **Interpretation of results and aetiology***

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%), hypomagnesuria (7-23%), and hypocitraturia (5-29%). However, ranges tend to differ based on ethnicity [624].

- Elevated levels of ionised calcium in serum (or total calcium and albumin) require assessment of intact PTH to confirm or exclude suspected hyperparathyroidism (HPT).
- Consistently low pH (< 5.5) or 24-hour urine pH < 5.5 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.
- A pH > 6.2 in a 24-hour urine collection may indicate RTA provided UTI has been excluded. An ammonium chloride loading test confirms distal RTA (Section 4.6.5).
- Hypercalciuria may be associated with normocalcemia (idiopathic hypercalciuria, or granulomatous diseases) or hypercalcemia (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 confirms hyperoxaluria (see Table 4.3 for the values in children).
    - primary hyperoxaluria (oxalate excretion mostly > 1 mmol/day), appears in three genetically determined forms;
    - secondary hyperoxaluria (oxalate excretion > 0.5 mmol/day, usually < 1 mmol/day), occurs due to intestinal hyperabsorption of oxalate or extreme dietary oxalate intake;
    - mild 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 4.3: 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) or (thiazide + allopurinol) is superior to thiazide therapy alone [588, 625].*

5 *Febuxostat 80 mg/d.*

* *Low evidence (see text)*

** *Calciuria is a continuous variable and treatment may be adjusted to clinical need even when below the threshold indicated.*

*** *Patients on hydrochlorothiazide should be advised to get their skin checked on a regular basis as they have a higher risk of developing NMSC and some forms of melanoma. In patients with a history of skin cancer, the indication for treatment with hydrochlorothiazide should be thoroughly reviewed [621-623].*

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 4.3 summarises the pharmacological treatment of calcium oxalate stones [557, 564, 587-590, 593, 594, 596, 600, 603-605, 609-616, 624, 626-629]. There is only low-level evidence for the efficacy of preventing stone recurrence based on pre-treatment stone composition examination and biochemistry measures, or on-treatment biochemistry measures [557]. One RCT concluded that treatment with hydrochlorothiazide (HCTZ) does not differ substantially from placebo in the prevention of stone recurrence of kidney stones in patients at high risk for recurrence [630]. However, the study was not powered to show any difference of HCTZ over placebo [631]. In fact, the study's main objective based on the author's protocol [631], was to investigate the existence of a dose-response relationship, i.e., a linear trend for three different doses of HCTZ (12.5, 25 mg, and 50 mg/day) on stone recurrence, and this was shown. In addition, the hypercalciuria levels in the population enrolled in the study were significantly lower than the threshold the EAU guidelines recommend being administered to patients (Figure 4.3).

4.4.4 Summary of evidence and recommendations for pharmacological treatments for patients with specific abnormalities in urine composition (based on 24-hour urine samples)

Summary of evidence	LE
Alkaline citrates can reduce stone formation.	1a
Thiazides reduces calciuria.	1a
Oxalate restriction is beneficial if hyperoxaluria is present.	2b
Alkaline citrates can reduce stone formation in enteric hyperoxaluria.	4
Calcium supplement can reduce stone formation in enteric hyperoxaluria.	2
A diet reduced in fat and oxalate can be beneficial in reducing stone formation.	3
Alkaline citrates and sodium bicarbonate can be used if hypocitraturia is present.	1b
Allopurinol is first-line treatment of hyperuricosuria.	1a
Febuxostat is second-line treatment of hyperuricosuria.	1b
Avoid excessive intake of animal protein in hyperuricosuria.	1b
Restricted intake of salt is beneficial if there is high urinary sodium excretion.	1b

Recommendations	Strength rating
Prescribe thiazide or alkaline citrates or both in case of hypercalciuria*.	Strong
Advise oxalate restriction if hyperoxaluria is present.	Weak
Offer alkaline citrates in enteric hyperoxaluria.	Weak
Offer calcium supplement in enteric hyperoxaluria.	Strong
Advise reduced dietary fat and oxalate in enteric hyperoxaluria.	Weak
Prescribe alkaline citrates or sodium bicarbonate in case of hypocitraturia.	Strong
Prescribe allopurinol in case of hyperuricosuria.	Strong
Offer febuxostat as second-line treatment of hyperuricosuria.	Strong
Avoid excessive intake of animal protein in hyperuricosuria.	Strong
Advise restricted intake of salt if there is high urinary sodium excretion.	Strong

** Patients on hydrochlorothiazide should be advised to get their skin checked on a regular basis as they have a higher risk of developing an NMSC and some forms of melanoma. In patients with a history of skin cancer, the indication for treatment with hydrochlorothiazide should be thoroughly reviewed [621-623].*

4.5 Calcium phosphate stones [557, 587, 596, 609, 610, 614, 632]

Some calcium phosphate stone formers are at high risk of recurrence. Further information on identifying high-risk patients is provided in section 3.1.3.

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.

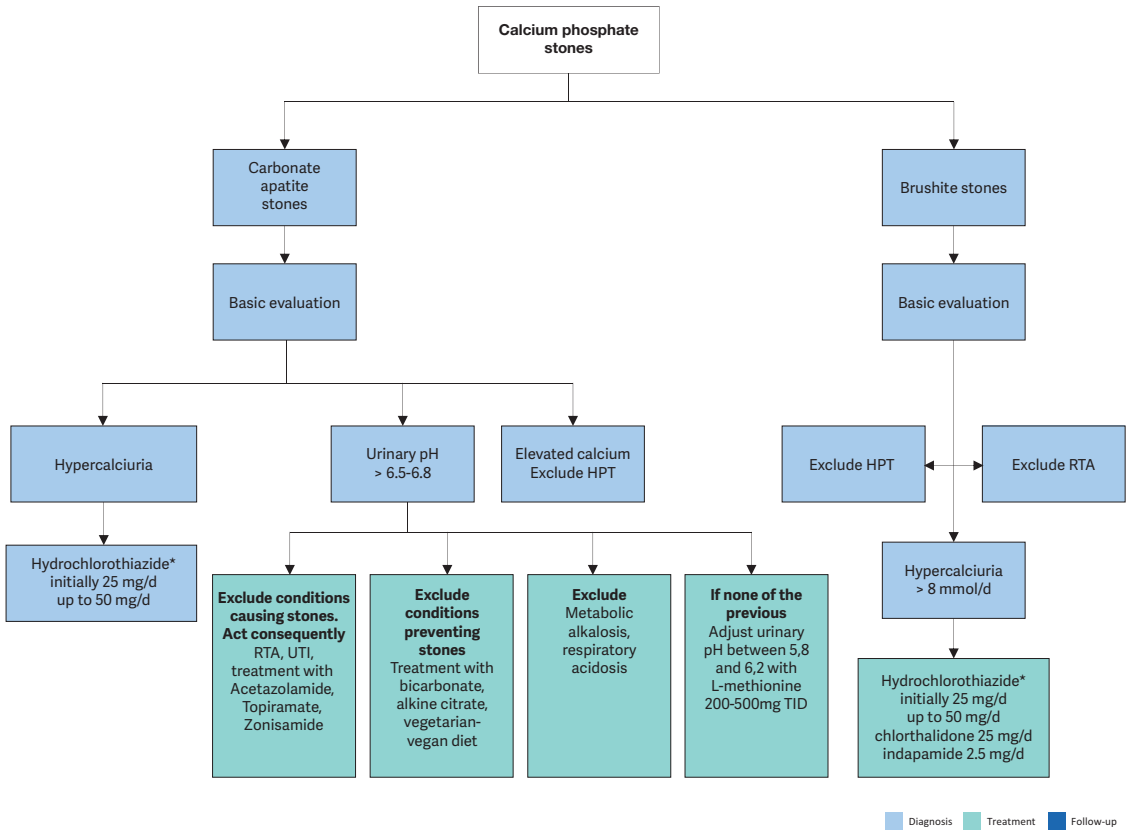
*4.5.1 **Diagnosis***

Diagnosis requires blood analysis for creatinine, sodium, potassium, chloride, ionised calcium (or total calcium + albumin), phosphate, and PTH (in the case of increased calcium levels). Urinalysis includes measurement of volume, urine pH, 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 4.4.

Figure 4.4: Diagnostic and therapeutic algorithm for calcium phosphate stones



HPT = hyperparathyroidism; RTA = renal tubular acidosis; UTI = urinary tract infection.

** Patients on hydrochlorothiazide should be advised to get their skin checked on a regular basis as they have a higher risk of developing NMSC and some forms of melanoma. In patients with a history of skin cancer, the indication for treatment with hydrochlorothiazide should be thoroughly reviewed [621-623].*

*4.5.3 **Pharmacological therapy*** [557, 587, 596, 609, 610, 614, 632]

Hyperparathyroidism and RTA are common causes of calcium phosphate stone formation. Most patients with primary HPT require surgery. Renal tubular acidosis can be corrected pharmacologically including with bicarbonate or alkaline citrate therapy. If primary HPT and RTA have been excluded, pharmacotherapy for calcium phosphate calculi depends on the effective reduction of urinary calcium levels using thiazides. For infection-associated calcium phosphate stones, it is important to consider the guidance given for infection stones.

4.5.4 Summary of evidence and recommendation for the management of calcium phosphate Stones

Summary of evidence	LE
Thiazide decreases calciuria.	1a

Recommendation	Strength rating
Prescribe thiazide in case of hypercalciuria > 8 mmol/24 hours.	Strong

4.6 Disorders and diseases related to calcium stones

*4.6.1 **Hyperparathyroidism** [633-636]*

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 hypercalcemia, hypercalciuria, and bone disease. 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. Nephrocalcinosis and CKD may also occur.

If HPT is suspected, neck exploration should be performed to confirm the diagnosis. If surgery is contraindicated, primary HPT can be treated with cinacalcet.

*4.6.2 **Granulomatous Diseases** [637]*

Granulomatous diseases, such as sarcoidosis, may be complicated by hypercalcemia 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 focuses on the activity of the granulomatous diseases and may require steroids, hydroxychloroquine, or ketoconazole. Treatment should be reserved for a specialist.

*4.6.3 **Primary Hyperoxaluria** [606]*

Patients with primary hyperoxaluria (PH) should be referred to a specialised center, 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 hyper-diuresis, alkaline citrates, magnesium, and Lumasiran, an RNAi agent, a new treatment for reducing the synthesis of oxalate of PH type 1 [638].

Treatment regimens are:

- pyridoxine in PH type I: 5-20 mg/kg/day according to urinary oxalate excretion and patient tolerance;
- alkaline citrate: 3.25-9.75 g/day in adults, 0.1-0.15 mq/kg/day in children;
- magnesium: 200-400 mg/day (no magnesium in the case of renal insufficiency).
- Lumasiran: Subcutaneous injection with dose and timing adjusted according to body weight and duration of treatment:
    - Initial Dose: Bodyweight < 10 kg: 6 mg/kg; Bodyweight 10-20 kg: 6 mg/kg; Bodyweight > 20 kg: 3 mg/kg; once per month for three months subcutaneous injection.
    - Maintenance starting one month after initial doses: Bodyweight < 10 kg: 3 mg/kg 1-mal monthly; Bodyweight 10-20 kg: 6 mg/kg every three months, Bodyweight > 20 kg: 3 mg/kg [639]

4.6.3.1 Summary of evidence and recommendation for the management of primary hyperoxaluria

Summary of evidence	LE
Pyridoxine can reduce the urinary oxalate excretion in primary hyperoxaluria type 1.	3
Lumasiran can reduce the urinary oxalate excretion in primary hyperoxaluria type 1.	1b

Recommendation	Strength rating
Prescribe pyridoxine for primary hyperoxaluria type 1.	Strong
Prescribe Lumasiran for primary hyperoxaluria type 1 if not responsive to pyridoxine.	Strong

*4.6.4 **Enteric hyperoxaluria** [575, 580, 640-642]*

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, as well as 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, stone formation, and less frequently to nephrocalcinosis and CKD. Specific preventive measures are:

- restricted intake of oxalate-rich foods [575];
- restricted fat intake [575];
- calcium supplementation at mealtimes to enable calcium oxalate complex formation in the intestine [580, 640-642];
- sufficient fluid intake to balance the intestinal loss of water caused by diarrhoea;
- alkaline citrates to raise urinary pH and citrate.

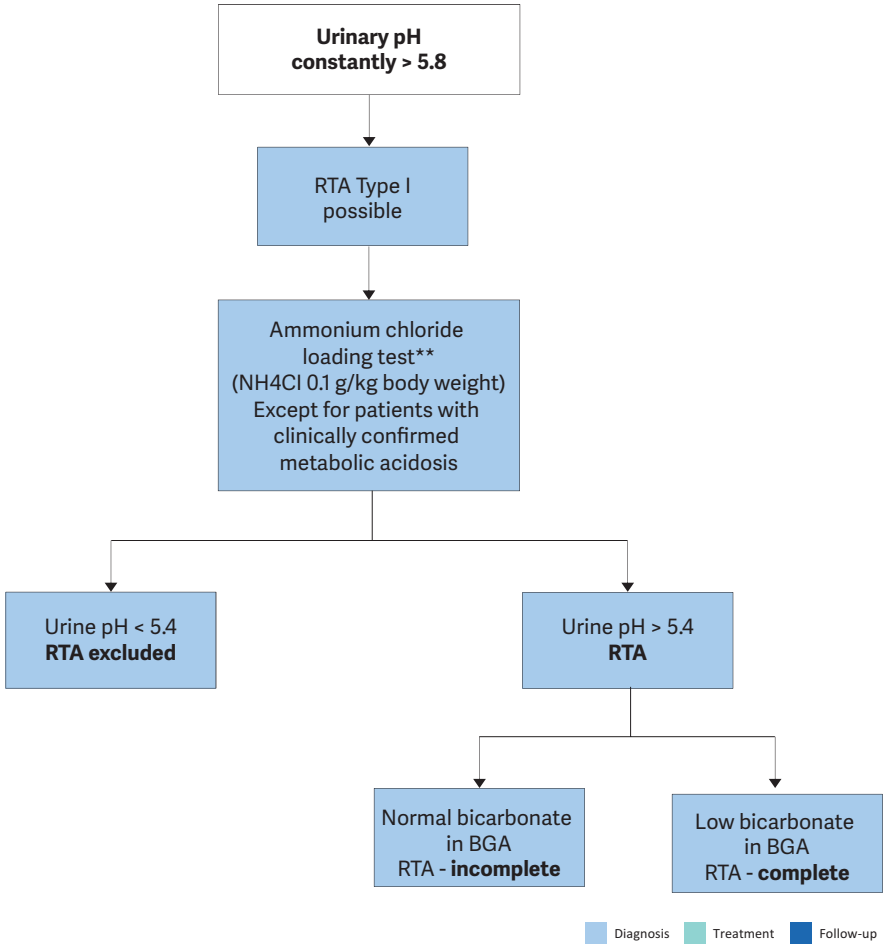
Summary of evidence	LE
Alkaline citrates can be beneficial to replace citrate loss and raise urine pH.	3
Calcium supplements with meals enable calcium oxalate complex formation in the intestine.	2b
Reduction in dietary fat and oxalate can be beneficial in intestinal malabsorption.	3

Recommendations	Strength rating
Prescribe alkaline citrates for enteric hyperoxaluria.	Weak
Advise patients to take calcium supplements with meals.	Strong
Advise patients to follow a diet with a low fat and oxalate content.	Weak

*4.6.5 **Renal tubular acidosis** [557, 596, 643, 644]*

Renal tubular acidosis is caused by severe impairment of proton (type I) or bicarbonate handling (type II) along the nephron. Kidney stone formation occurs in patients with distal RTA type I. Figure 4.5 outlines the diagnosis of RTA type I. Table 4.7 shows acquired and inherited causes of RTA.

Figure 4.5: Diagnosis of renal tubular acidosis



BGA = blood gas analysis; RTA = renal tubular acidosis.
*** An alternative ammonium chloride loading test using 1-day NH4Cl load with 0.05 g/kg body weight might provide similar results and may be better tolerated by the patient [645]. A second alternative in these cases could be the furosemide/fludrocortisone acidification test [646].*

Renal tubular acidosis can be acquired or inherited. Reasons for acquired RTA can be chronic obstructive uropathy, recurrent pyelonephritis, acute tubular necrosis, renal transplantation, analgesic nephropathy, sarcoidosis, Sjögren syndrome and other autoimmune diseases, medullary sponge kidney, liver cirrhosis, sickle cell anaemia, idiopathic hypercalciuria, and primary parathyroidism; it may also be drug-induced (e.g., amphotericin B, foscarnet, lithium, zonisamide, and other carbonic anhydrase inhibitors).

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, rickets/osteomalacia
Autosomal recessive with hearing loss	ATP6V1B1/B1 sub-unit of vacuolar H-ATPase/proton secretion	Hypercalciuria, hypokalaemia, rickets/osteomalacia
Autosomal recessive	ATP6V0A4/A4 sub-unit of vacuolar H-ATPase/proton secretion	Hypercalciuria, hypokalaemia, rickets/osteomalacia

Very rarely biallelic causative variants in FOXI1 and WDR72 genes have also been identified. The main therapeutic aim of RTA treatment is restoring a normal acid-base equilibrium. Despite the alkaline pH of urine in RTA, alkalinisation using alkaline citrates or sodium bicarbonate is important for normalising the metabolic changes (intracellular acidosis) responsible for stone formation (Table 4.8) and bone demineralisation. The alkali load reduces tubular re-absorption of citrate, which in turn normalises citrate excretion. 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	Indication 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	Citrate excretion male < 1.7 mmol/day, female < 1.9 mmol/day	Alkaline citrate, 3.25-9.75 g/day divided in three doses *OR* Sodium bicarbonate, 1.5 g, three times daily

** Patients on hydrochlorothiazide should be advised to get their skin checked on a regular basis as they have a higher risk of developing NMSC and some forms of melanoma. In patients with a history of skin cancer, the indication treatment with hydrochlorothiazide should be thoroughly reviewed [621-623].*

4.6.5.1 Summary of evidence and recommendations for the management of tubular acidosis

Summary of evidence	LE
Alkaline citrates can be beneficial in distal renal tubular acidosis.	2b
Thiazides are beneficial for hypercalciuria.	1a

Recommendations	Strength rating
Prescribe alkaline citrates for distal renal tubular acidosis.	Strong
Address normalization of bicarbonatremia and citraturia with alkaline citrate	Strong
Prescribe thiazides for hypercalciuria.	Strong

*4.6.6 **Nephrocalcinosis** [647]*

Nephrocalcinosis (NC) refers to increased calcium crystal deposition within the renal cortex or medulla and occurs alone or in combination with renal stones. There are various metabolic causes. The main causes are HPT, primary and enteric hyperoxalurias, genetic and acquired RTA, medullary sponge kidney, vitamin D metabolic disorders, sarcoidosis, idiopathic hypercalciuria and hypocitraturia, and genetic disorders, including Dent's disease and Bartter's syndrome. The many causes of NC mean there is no single standard therapy. Therapeutic attention must focus on the underlying metabolic or genetic disease, on the frequent association with CKD 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 bicarbonate. Urinalysis should investigate urine pH profile at different times of the day daily urine volume, specific weight of urine, and levels of calcium, oxalate, phosphate, uric acid, magnesium, and citrate [545].

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 [23]. Uric acid nephrolithiasis is responsible for approximately 10% of renal stones [648] and is associated with hyperuricosuria or low urinary pH. Hyperuricosuria may be a result of dietary excess, endogenous overproduction (enzyme defects), myeloproliferative disorders, chemotherapy drugs, gout or catabolism [542]. Low urinary pH may be caused by decreased urinary ammonium excretion (insulin resistance, gout, Autosomal dominant polycystic kidney disease [ADPKD]), 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) [542].

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), phosphate deficiency, hypokalemia, and malnutrition. Suggestions on uric acid and ammonium urate nephrolithiasis are based on level 3 and 4 evidence. Chronic kidney disease is frequently observed.

*4.7.1 **Diagnosis***

Figure 4.6 shows the diagnostic algorithm for uric acid stones and figure 4.7 shows the therapeutic algorithm for uric acid and ammonium urate stones. Blood analysis requires measurement of creatinine and uric acid levels. Urinalysis requires measurement of urine volume, urine pH, 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. Low urine pH promotes uric acid crystallisation.

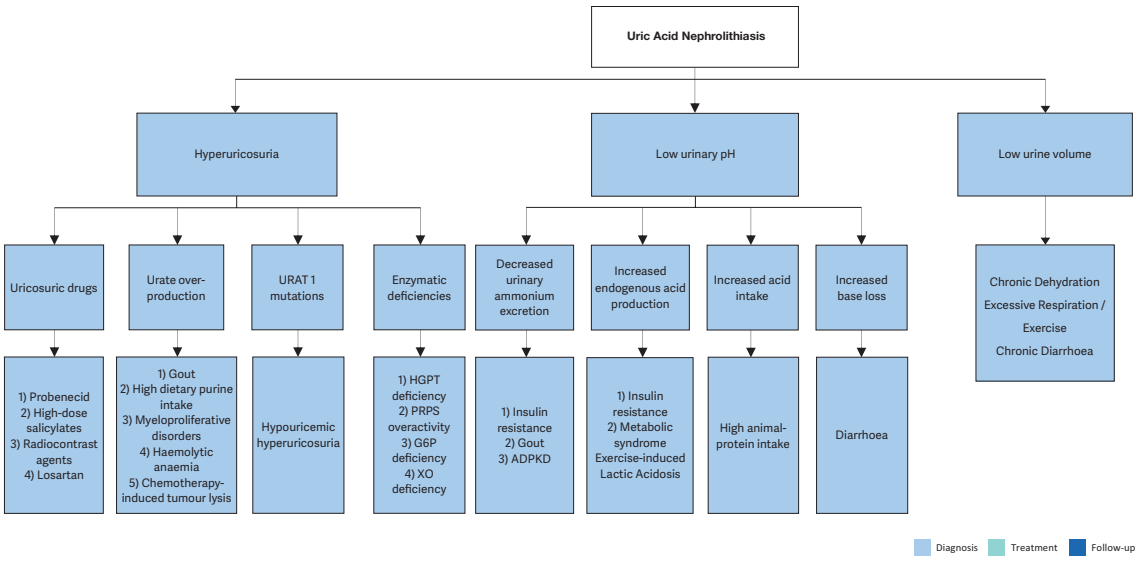
Hyperuricosuria is defined as uric acid excretion > 4 mmol/day and day and > 5 mmol/day in adult females and males, respectively, or > 0.12 mmol/kg/day in children. Hyperuricaemia may be present, but there is only weak evidence for its association with stone formation [649].

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 [650, 651]. Ammonium urate crystals form in urine at pH > 6.5, high uric acid concentration in urine when ammonium is present [652, 653].

*4.7.3 **Specific treatment***

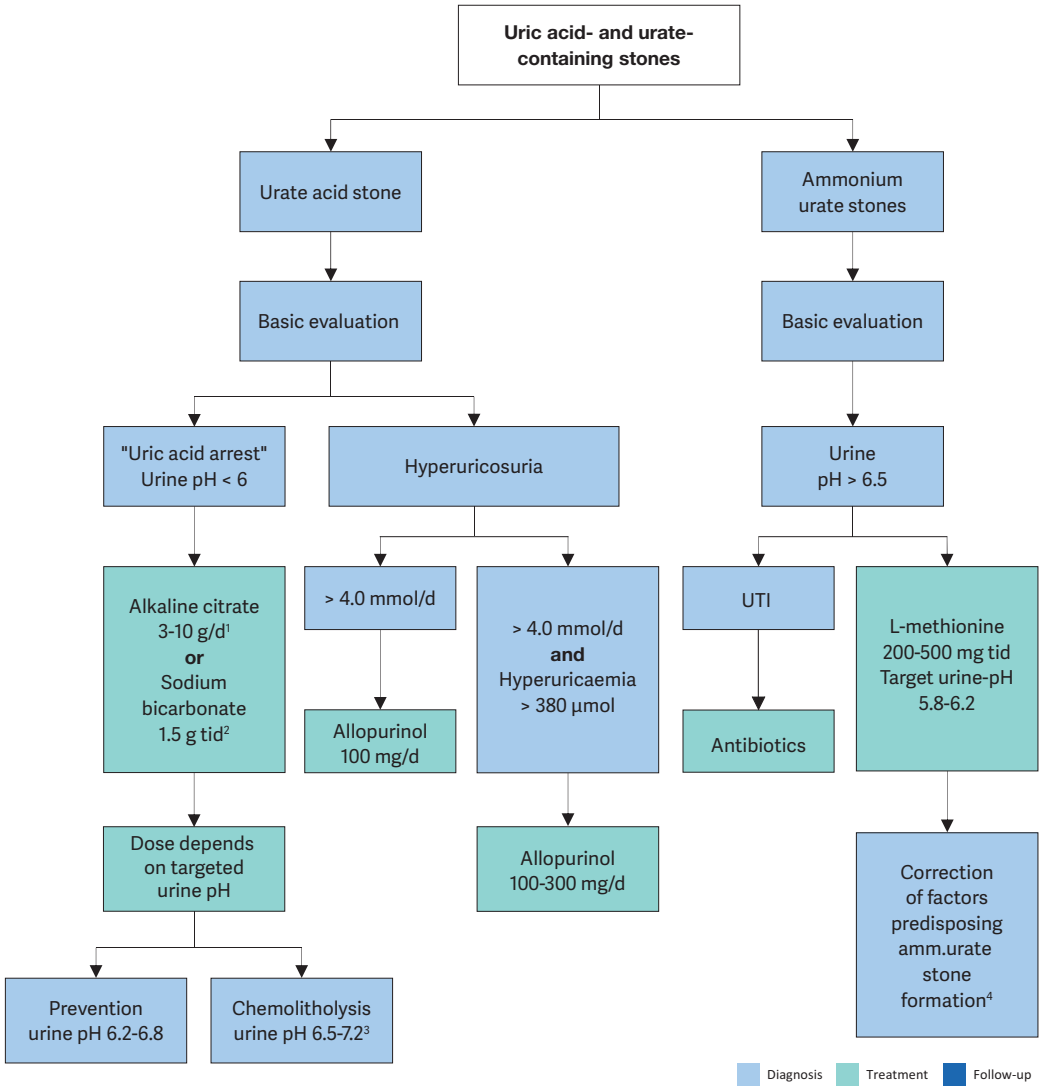
General preventive measures are recommended for fluid intake and diet. Hyperuricosuric stone formers benefit from purine reduction in their daily diet. Figure 4.6 describes pharmacological treatment [23, 648, 650-660]. For uric acid stones, allopurinol may change the stone composition distribution in patients with gout to a pattern similar to that in stone formers without gout [661].

Figure 4.6: Diagnostic algorithm for uric acid stones



ADPKD = autosomal dominant polycystic kidney disease; G6P = glucose-6 phosphate dehydrogenase; HGPT = hypoxanthine guanine phosphoribosyl transferase; PRPS = phosphoribosyl-pyrophosphate synthetase superactivity; XO = xanthine oxidase.

Figure 4.7: 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.*

4.7.4 Summary of evidence and recommendations for the management of uric acid- and ammonium urate stones

Summary of evidence	LE
Alkaline citrates can be beneficial to alkalinise the urine in uric acid stone formers.	3
Allopurinol can be beneficial in hyperuricosuric urate stone formers.	1b

Recommendations	Strength rating
Prescribe alkaline citrates to alkalinise the urine in uric acid stone formers.	Strong
Prescribe allopurinol in hyperuricosuric urate stone formers.	Strong

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 [662]. There are several factors predisposing patients to struvite stone formation (Table 4.9) [663]. Several studies have reported that urinary metabolic alterations can be disclosed in 36-81% of patients with mixed struvite stones [664-669].

*4.8.1 **Diagnosis***

Blood analysis requires measurement of creatinine, and urinalysis requires repeat urine pH measurements and urine culture. In cases of mixed struvite stones, the search for metabolic abnormalities in 24-hour urine after stone removal and infection control is suggested.

*4.8.2 **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 [670, 671]. A mixed struvite stone, i.e., containing a high percentage of calcium oxalate and carbonate apatite, suggests the over-infection of a "metabolic" calcium oxalate or calcium phosphate stone [669]. Proteus mirabilis accounts for more than half of all urease positive UTIs [672, 673].

*4.8.3 **Specific treatment***

General preventive measures are recommended for fluid intake and diet. Specific measures include complete surgical stone removal [663], short- or long-term antibiotic treatment [674], and urinary acidification using methionine [602] or ammonium chloride [675]. For persistent infections/colonisation, acetohydroxamic acid may be an option [676, 677] (Figure 4.8); however, it is not licensed/available in all European countries.

Eradication of infection after complete stone removal is desirable. The evidence regarding the duration of post-operative antibiotic administration is inconclusive.

Summary of evidence	LE
Removing the stone material as completely as possible with surgery can reduce ongoing infection.	3
Antibiotics are beneficial after complete stone removal.	3
Ammonium chloride, 1 g, two or three times daily, can ensure urinary acidification to prevent recurrent infection.	3
Methionine, 200-500 mg, one to three times daily, can be used as an alternative to ammonium chloride, to ensure urinary acidification.	3
Treatment of underlying metabolic abnormalities reduces recurrence of mixed struvite stones.	3
Urease inhibitors in case of severe infection are occasionally used (if licensed).	1b

Recommendations	Strength rating
Surgically remove the stone material as completely as possible.	Strong
Prescribe antibiotics in case of persistent bacteriuria.	Strong
Prescribe ammonium chloride, 1 g, two or three times daily to ensure urinary acidification.	Weak
Prescribe methionine, 200-500 mg, one to three times daily, as an alternative, to ensure urinary acidification.	Weak

Table 4.9: Factors predisposing to struvite stone formation.

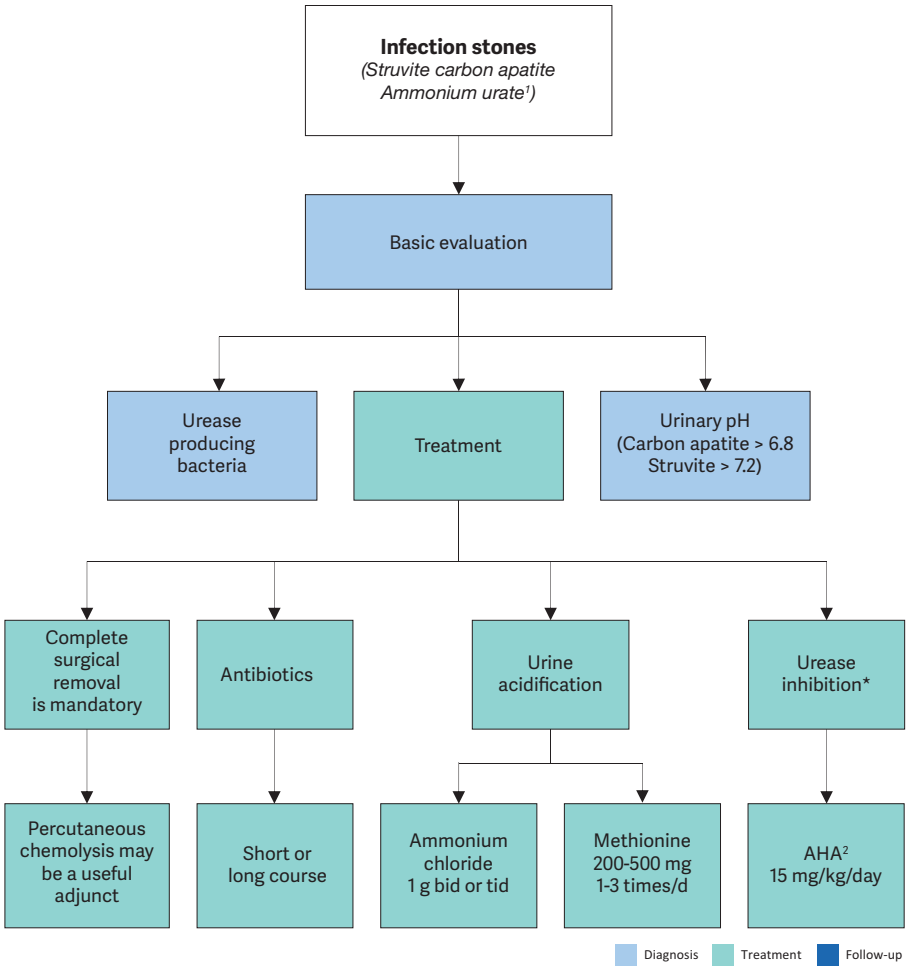
• Neurogenic bladder • Spinal cord injury/paralysis • Continent urinary diversion • Ileal conduit • Foreign body • Stone disease • Indwelling urinary catheter	• Urethral stricture • Benign prostatic hyperplasia • Bladder diverticulum • Cystocele • Calyceal diverticulum • UPJ obstruction

Table 4.10: Most important species of urease-producing bacteria

Obligate urease-producing bacteria (> 98%)
• *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 4.8: Diagnostic and therapeutic algorithm for infection stones.



[1] *Discussed with uric acid stones.*
[2] *Acetohydroxamic acid.*
** When nationally available.*
bid = twice a day; tid = three times a day; AHA = acetohydroxamic acid.

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 [678, 679]. All cystine stone formers are deemed at high risk of recurrence and CKD [680, 681].

*4.9.1 **Diagnosis***

Blood analysis includes measurement of creatinine, and urinalysis includes measurement of urine volume, pH profile, specific weight, and cystine. Since the disease may be asymptomatic, siblings of cystinuric patients should be investigated for cystinuria [682].

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 the phenotype or genotype of the cystinuric patient, the clinical manifestations are the same [683].
- There is no role for genotyping patients in the routine management of cystinuria [684, 685].
- Reductive therapy targets the disulphide binding in the cystine molecule. For therapy monitoring, it is important to differentiate between cystine, cysteine, and drug-cysteine complexes. However, available methods to monitor cystinuria treatment which may be able to differentiate between the different complexes formed by therapy are cumbersome [686, 687] non accurate, including high-performance liquid chromatography (HPLC) [63].
- Quantitative 24-hour urinary cystine excretion confirms the diagnosis in the absence of stone analysis.
- Levels above 0.125 mmol/day (30 mg/day) are considered abnormal [688, 689].

*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 (5 g NaCl) [690]. A high level of diuresis is of fundamental importance, aiming for a 24-hour urine volume of > 3 L [683, 690-692]. A considerable fluid intake evenly distributed throughout the day is necessary.

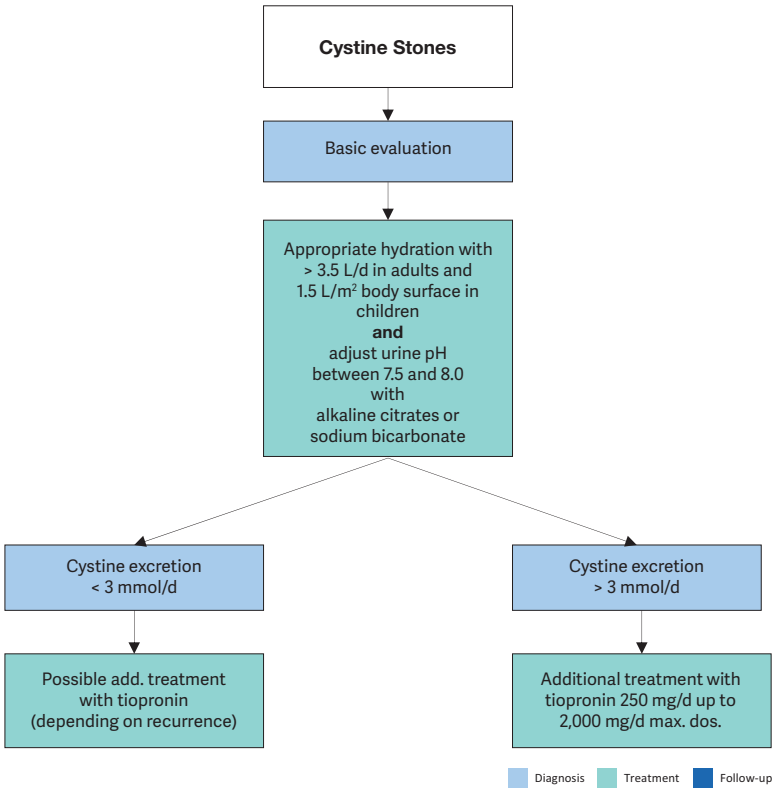
4.9.2.1 Pharmacological treatment of cystine stones

The main therapeutic option for avoiding cystine crystallisation is to maintain urine pH > 7.5, to improve cysteine solubility, and ensure appropriate hydration with a minimum of >3 L/day in adults, or 1.5 L/m2 body surface area in children [683, 690-692]. Home monitoring of the urine pH is suggested because of the possibility of self-adjusting alkaline treatment keeping the urine pH within range [63].

Free cystine concentration can be decreased by reductive substances, which act by splitting the disulphide binding of cystine.

Tiopronin is currently the best choice for cystine reduction. However, side effects often lead to treatment termination, for example when nephrotic syndrome develops or when there is 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 (720 mg/day) or in the case of recurring stone formation, notwithstanding other preventive measures [683, 690-692]. Spot measurement of urine protein should be performed at baseline and during follow-up.

Figure 4.9: Metabolic management of cystine stones [693]



4.9.3 Summary of evidence and recommendations for the management of cystine stones

Summary of evidence	LE
Increasing fluid intake so that 24-hour urine volume exceeds 3 L is used to dilute the cystine.	3
Alkaline citrates 3-10 mmol two or three times daily can be used to achieve pH > 7.5.	3
Tiopronin, 250-2,000 mg/day can be used to reduce stone formation in patients with cysteine excretion, > 3 mmol/day, or when other measures are insufficient.	3

Recommendations	Strength rating
Therapeutic measures	
Urine dilution Advise patients to increase their fluid intake so that 24-hour urine volume exceeds 3 L.	Strong
Alkalinisation Prescribe potassium citrate 3-10 mmol two or three times daily, to achieve pH > 7.5	Strong
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.	Strong

4.10 2,8-Dihydroxyandenine stones and xanthine stones

All 2,8-Dihydroxyadenine and xanthine stone formers are at high risk of recurrence. Both stone types are rare. Diagnosis and specific prevention are similar to those for uric acid stones [23].

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 [694]. High-dose allopurinol or febuxostat are important options but should be given with regular monitoring [695].

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 (urine specific gravity). A purine-reduced diet decreases the risk of spontaneous crystallisation in urine.

4.11 Drug-induced stones

Drug stones are induced by pharmacological treatment [587, 696] (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	Substances impairing urine composition
• Allopurinol/oxypurinol • Amoxicillin/ampicillin • Ceftriaxone • Quinolones • Ephedrine • Indinavir and other HIV-protease inhibitors • Magnesium trisilicate • Sulphonamides • Triamterene	• Acetazolamide • Aluminium magnesium hydroxide • Ascorbic acid • Calcium • Laxatives • Losartan • Methoxyflurane • Orlistat • Vitamin D • Topiramate • Zonisamide

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 *P. mirabilis* or *E. 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 [697].

4.13 Unknown stone composition [16]

An accurate medical history is the first step towards identifying risk factors as summarised in sections 3.1.3 and 4.13.1 and Fig. 4.1.

Diagnostic imaging begins with a US examination of both kidneys to establish whether the patient is stone-free. Stone detection by the US should be followed by KUB and unenhanced multislice CT in adults to differentiate between calcium-containing and non-calcium stones.

Blood analysis may demonstrate severe metabolic and organic disorders, such as renal insufficiency, HPT or other hypercalcaemic states and hyperuricaemia. In children with GFR lower than 30 ml/min, oxalaemia should also be checked.

Urinalysis is performed routinely with a dipstick test as described above. A urine culture is required if there are signs of infection. Urine pH < 5.5 in 24-hour urine collection indicates hyper-acidic urine, which could promote uric acid crystallisation. Urine pH > 6.2 in 24-hour urine collection may indicate RTA if UTI is excluded [642, 644].

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 [698, 699].

Following this programme, the most probable stone type can be assumed, and specific patient evaluation can follow. Further metabolic investigations will depend on the presence of risk factors (see section 3.1.3) and on the results of previous investigations. However, if any expulsed stone material is available, it should be analysed for diagnostic confirmation or correction.

*4.13.1 **Recommendations for investigations for the assessment of patients with stones of unknown composition** [17, 23, 62, 587]*

Recommendations		**Strength rating**
Investigation	**Rationale for investigation**	
Take a medical history	• Stone history (former stone events, family history) • Dietary habits • Medication chart	Strong
Perform diagnostic imaging	• Ultrasound in the case of a suspected stone • Un-enhanced helical computed tomography • Determination of Hounsfield units provides information about the possible stone composition	Strong
Perform a blood analysis	• Creatinine • Calcium (ionised calcium or total calcium + albumin) • Uric acid	Strong
Perform a urinalysis	• pH measurement • Dipstick test: leukocytes, erythrocytes, nitrites • Protein, 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.	Strong

5. FOLLOW-UP OF URINARY STONES

There is no consensus in the urological literature on whether, when, how, and how often stone patients should be followed up after definitive treatment (extracorporeal shock wave lithotripsy, ureteroscopy, percutaneous nephrolithotripsy, medical chemoprophylaxis). This is mainly attributed to the high heterogeneity of stone disease among patients and to the lack of comparative studies regarding follow-up versus no follow-up.

The EAU Urolithiasis Guidelines Panel performed a systematic review questioning the benefits and harms of scheduled imaging and metabolic follow-up for patients who underwent definitive treatment for upper urinary tract stone disease [411]. Based on the results a consensus was reached regarding the frequency of the follow-up for stone-free patients (the general population and the high-risk patients), patients with residual fragments ≤ 4 mm, and patients with residual fragments > 4 mm (Figures 5.1 and 5.2).

Stone-free patients could be discharged after two years (radiopaque stones) or after three years (radiolucent stones) as 80% of them will remain stone-free thereafter. Increasing the safety margin for remaining stone-free up to 90%, the patients should be followed up to five years. Most stone-free patients in the general population remained stone-free during the first year, while < 40% of patients with metabolic abnormalities not on medication remained stone-free after three years of follow-up. Therefore, a more extensive follow-up is proposed for patients with metabolic abnormalities.

Patients with fragments ≤ 4 mm showed a spontaneous expulsion rate of 17.9-46.5% during the first year. At 49 months of follow-up disease progression rate was 9-34%, the intervention rate 17-29%, and the spontaneous passage rate 21-34%.

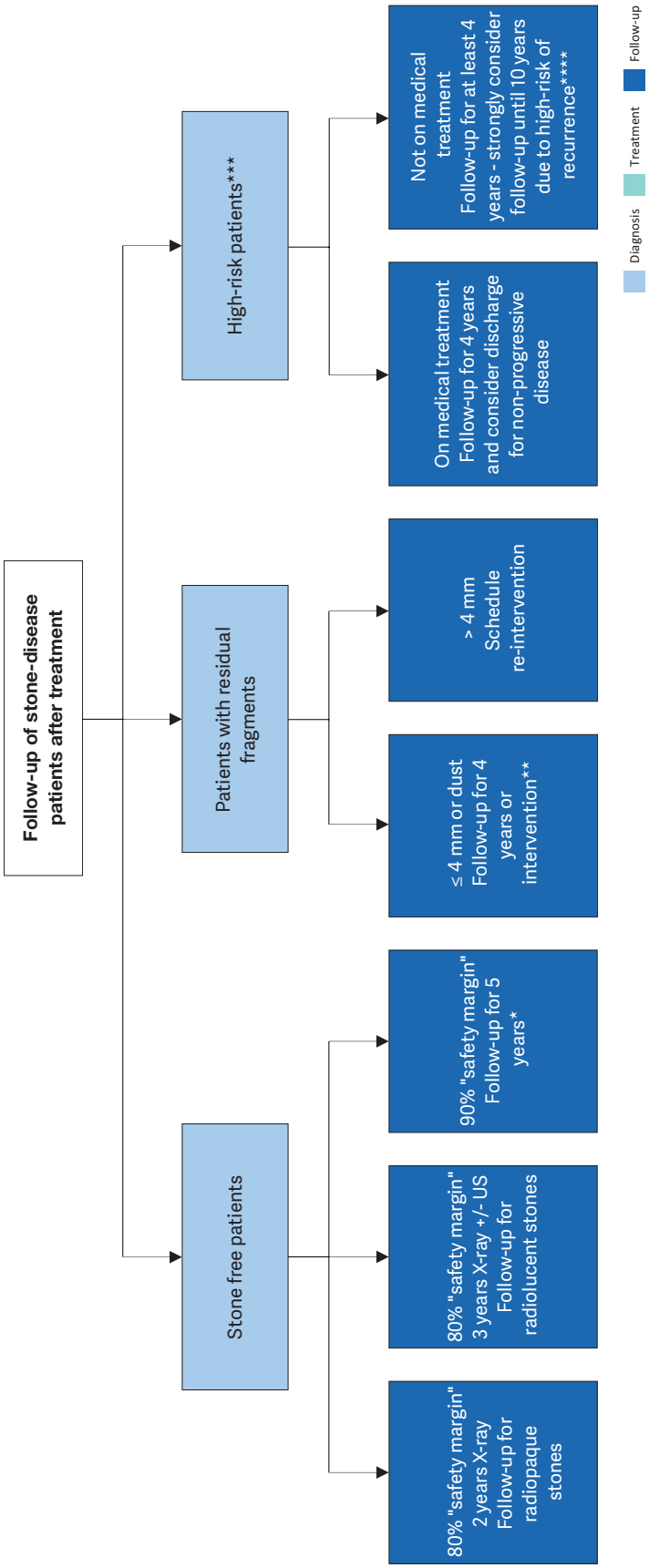
Patients with residual stone fragments > 4 mm had only 9% of spontaneous expulsion at three years. These patients should be offered further definitive treatment since intervention rates are high (24-100%). For those on follow-up close surveillance is needed.

Insufficient data exist for high-risk patients, but current literature dictates that patients who are adherent to targeted medical treatment seem to experience less stone growth or re-growth of residual fragments and may be discharged after 36-48 months of non-progressive disease on imaging (Figure 5.1).

Proposed imaging consists of plain X-ray KUB and/or US, based on stone characteristics and clinicians' preferences. Computed tomography scan should be reserved for symptomatic disease or pre-operative imaging, to avoid extensive radiation exposure [411].

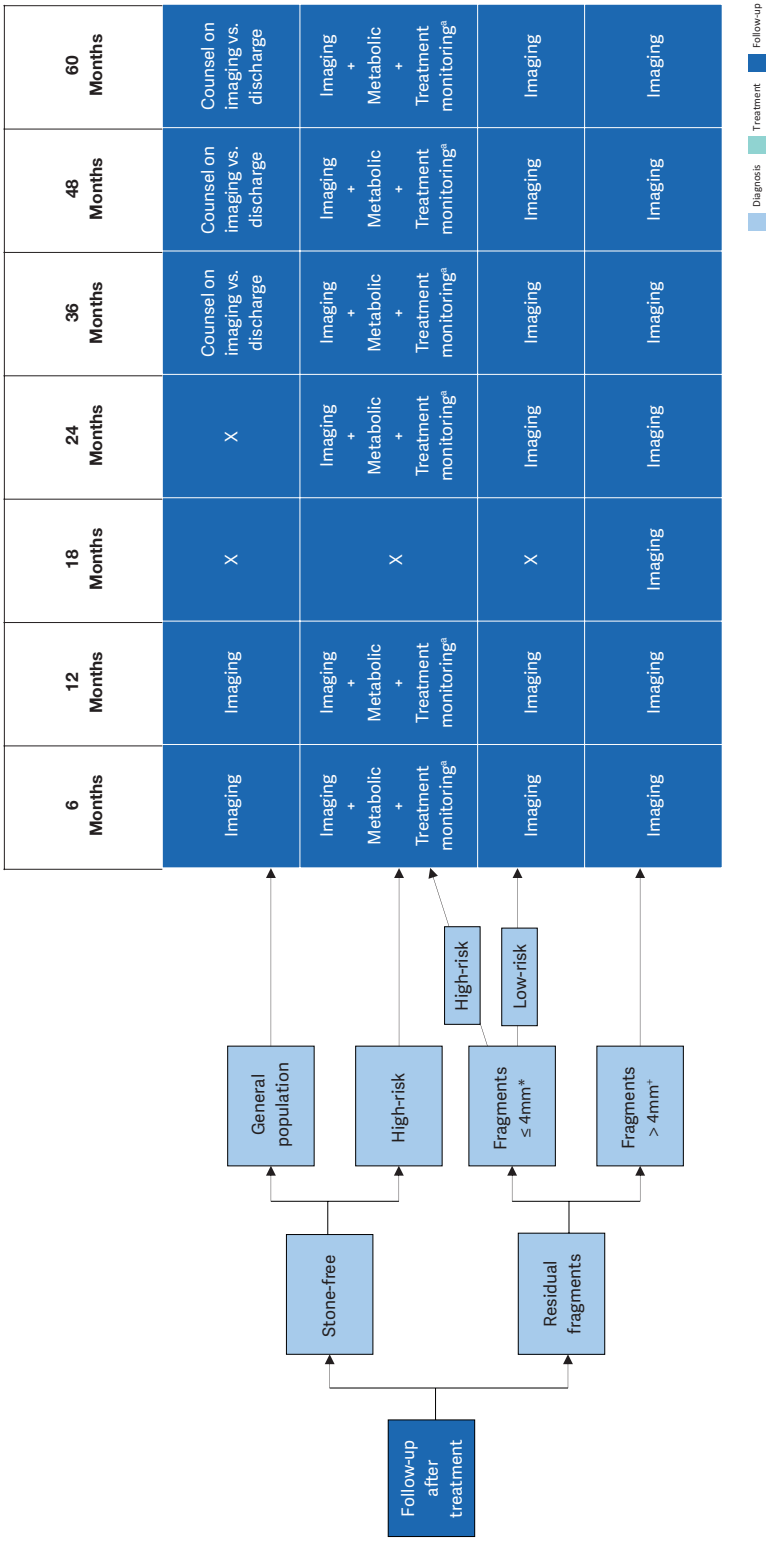
The information on stone composition can be used to counsel patients to set expectations and help plan the need for follow up and medical stone management [700].

Figure 5.1: Follow-up duration of Urinary stone patients after treatment.



** Not enough data about subgroup analysis of radiolucent and radiopaque stones.*
***According to patient preference or symptomatic disease.*
****Patients with diagnosed metabolic abnormalities.*
*****Lifelong follow-up is advised but data are available for up to ten years.*

Figure 5.2: Consensus on follow-up frequency and imaging modality to use after treatment



Stone free = No stone fragments on postoperative imaging (i.e. no stone fragments on CT/KUB/US).
High-Risk = Known biochemical abnormality (i.e.: hypercalciuria, hypocitraturia, hyperuricosuria, RTA, or high-risk stone type such as struvite [See table 3.6]).
Imaging = plain film KUB &/or kidney ultrasonography (KUS) based on clinicians' preference and stone characteristics. Consider CT if the patient is symptomatic or if intervention is planned.

** Clinicians may choose the imaging-only pathway in patients with fragments ≤ 2 mm.*
a Treatment monitoring for side effects, intolerance, and compliance.
+ Panel recommends reintervention however close follow up may be considered for some patients at high risk for reintervention based on clinicians' preference.

6. BLADDER STONES

6.1 Prevalence, aetiology, and risk factors of bladder stones

Bladder stones constitute only approximately 5% of all urinary tract stones [701] yet are responsible for 8% of urolithiasis-related mortalities in developed nations [702]. The incidence is higher in developing countries [703]. The prevalence of bladder stones is higher in males, with a reported male-to-female ratio between 10:1 and 4:1 [704, 705]. The age distribution is bimodal: incidence peaks at three years in children in developing countries [704, 706], and 60 years in adulthood [705].

The aetiology of bladder stones is typically multi-factorial [705]. Bladder stones can be classified as primary, secondary, or migratory [707].

Primary or endemic bladder stones occur in the absence of other urinary tract pathology, typically seen in children in areas with poor hydration, recurrent diarrhoea, and a diet deficient in animal protein [708].

Secondary bladder stones occur in the presence of other urinary tract abnormalities, which include bladder outlet obstruction (BOO), neurogenic bladder dysfunction, chronic bacteriuria, foreign bodies (including catheters), bladder diverticula, and bladder augmentation or urinary diversion. In adults, BOO is the most common predisposing factor for bladder stone formation and accounts for 45-79% of vesical calculi [705, 709-712].

Migratory bladder stones are those that have passed from the upper urinary tract where they formed and may then serve as a nidus for bladder stone growth. Patients with bladder calculi are more likely to have a history of upper tract stones and risk factors for their formation [713].

A wide range of metabolic urinary abnormalities can pre-dispose to calculi anywhere in the urinary tract, which is covered in more detail in Section 4. Metabolic Evaluation and Recurrence Prevention. There is a paucity of studies on the specific metabolic abnormalities that predispose to bladder stones.

Bladder stones will form in 3-4.7% of men undergoing surgery for benign prostatic obstruction (BPO) [714, 715], 19-39% and 36-67% of motor-incomplete and motor-complete spinal cord injury patients, respectively [716], and 2.2% of patients with long-term catheters [717]. Two research groups have identified that a larger intravesical protrusion of the prostrate is an independent risk factor for bladder stone formation in patients with BPH undergoing TURP [718, 719]. Kim and colleagues additionally found older age and a lower Qmax to be predictive of bladder stones [718].

In men with chronic urinary retention secondary to BPO, the 24-hour urine of 27 men with bladder stones had a higher uric acid supersaturation (2.2 vs. 0.6 mmol/L, $p < 0.01$), lower magnesium (106 vs. 167 mmol/L, $p = 0.01$) and lower pH (5.9 vs. 6.4, $p = 0.02$) than the 21 men without bladder stones [713]. It is therefore likely that patients with these conditions who form bladder stones also have an abnormal urine composition which predisposes them to bladder stone formation.

The metabolic abnormalities which predispose patients to form secondary bladder stones are poorly understood. Stone analysis of 86 men with a BPO-related bladder stone demonstrated that 42% had calcium-based stones (oxalate, phosphate), 33% had magnesium ammonium phosphate, 10% had mixed stones and 14% had urate stones [705]. Similar findings were reported in more recent studies [720-722] and it is therefore likely that multiple metabolic factors predispose patients to secondary bladder stone formation.

Low urine volume (poor hydration) is the most consistently demonstrable abnormality [723-725].

As an outlet obstruction is more often absent in children than in adults, the aetiology is most likely quite different in this population. Twenty-four-hour urine analysis in children with endemic bladder stones is reported in two studies. Of 57 children in Pakistan, 89.5% had hypocitraturia, 49% had a low urine volume, 44% had hyperoxaluria and 42% had hypocalciuria [723]. Of 61 children in India, stone formers had higher urine calcium and uromucoid concentrations than controls [724]. One study from Thailand compared 24-hour urine analyses from children from a rural area with a high prevalence of bladder stones with those from an urban area: rural children had lower urine volumes and, despite equal calcium, oxalate, and uric acid concentrations, crystalluria with uric acid and calcium oxalate crystals was more prevalent in rural children [725].

Table 6.1 Bladder stones classified by aetiology.

Type of bladder stone	Primary	Secondary	Migratory
Cause/Associations	Occur in the absence of other urinary tract pathology, typically in children in areas with poor hydration, recurrent diarrhoea, and a diet deficient in animal protein	BOO (e.g., BPO, urethral stricture)	Form in the upper urinary tract, then passed into the bladder where they may be a nidus for stone growth
		Neurogenic bladder dysfunction	
		Chronic bacteriuria	
		Foreign bodies (including catheters)	
		Bladder diverticula	
		Bladder augmentation	
		Urinary diversion	

BOO = Bladder Outlet Obstruction; BPO = Benign Prostatic Obstruction.

6.2 Presentation

The symptoms are most associated with bladder stones are urinary frequency, haematuria (which is typically terminal) and dysuria or suprapubic pain, which are worst towards the end of micturition. Sudden movement and exercise may exacerbate these symptoms. Detrusor over-activity is found in over two-thirds of adult male patients with vesical calculi and is significantly more common in patients with larger stones (> 4 cm). However, recurrent UTIs may be the only symptom [710, 711].

In children, symptoms may also include pulling of the penis, difficulties in micturition, urinary retention, enuresis, and rectal prolapse (resulting from straining due to bladder spasms). Bladder stones may also be an incidental finding in 10% of cases [708, 726].

6.3 Diagnostic evaluation

6.3.1 Diagnostic investigations for bladder stones

Plain X-ray of KUB has a reported sensitivity of 21%-78% for cystoscopically detected bladder stones in adults [710, 727]. Larger (> 2.0 cm) stones are more likely to be radiopaque [727]. However, plain X-ray provides information on radio-opacity which may guide treatment and follow-up (see Section 3.2.3 X-ray characteristics, for further information).

Ultrasound has a reported sensitivity and specificity of 20-83% and 98-100%, respectively for the detection of bladder stones in adults [728, 729]. Computed tomography and cystoscopy have a higher sensitivity for detecting bladder stones than US or X-ray in adults [728, 729]. No study compares cystoscopy and CT for the diagnosis of bladder stones. Cystoscopy has the advantage of detecting other potential causes for a patient's symptoms (e.g., bladder cancer), whilst CT can also assess upper tract urolithiasis (see also section 3.2.3 X-ray characteristics) [730].

There is a paucity of evidence for the investigation of bladder stones, particularly in children [83, 731]. See also Section 3.3 Diagnostic evaluation, for further information on diagnostic imaging for urolithiasis. The principle of ALARA should be applied, especially in children [732].

6.3.2 Diagnosing the cause of bladder stones

The cause of the bladder stone should be considered prior to bladder stone treatment as eliminating the underlying cause will reduce recurrence rates [733]. The following should be performed where possible prior to (or at the time of) bladder stone treatment:

- physical examination of external genitalia, and peripheral nervous system (including digital rectal examination, peri-anal tone, and sensation in men);
- uroflowmetry and post-void residual urine assessment;
- urine dipstick to include pH ± culture;
- metabolic assessment (see also section 3.3.2.3) including: serum (creatinine, (ionised) calcium, uric acid, sodium, potassium, blood cell count);
- urine pH;
- stone analysis: in first-time formers using a valid procedure (X-ray diffraction or infrared spectroscopy).

The following investigations should also be considered for selected patients:

- upper tract imaging (in patients with a history of urolithiasis or loin pain);
- cysto-urethroscopy or urethrogram.

6.4 Disease Management

*6.4.1 **Conservative treatment and Indications for active stone removal***

Migratory bladder stones in adults may typically be left untreated, especially asymptomatic small stones. Rates of spontaneous stone passage are unknown, but data on ureteric stones suggest stones < 1 cm are likely to pass in the absence of BOO, bladder dysfunction, or long-term catheterisation (see section 3.4.9 Specific stone management of ureteral stones).

Primary and secondary bladder stones are usually symptomatic and are unlikely to pass spontaneously: active treatment of such stones is therefore indicated.

*6.4.2 **Medical management of bladder stones***

There is a paucity of evidence on chemolitholysis of bladder stones. However, guidance on the medical management of urinary tract stones in section 3.4.9 Specific stone management of ureteral stones, can be applied to urinary stones in all locations. Uric acid stones can be dissolved by oral urinary alkalinisation when a PH > 6.5 is consistently achieved, typically using alkaline citrate or sodium bicarbonate. Regular monitoring is required during therapy (see section 3.4.4 Chemolysis). Irrigation chemolysis is also possible using a catheter; however, this is time-consuming may cause chemical cystitis and is therefore not commonly employed [734, 735].

*6.4.3 **Bladder stone interventions***

Minimally invasive techniques for the removal of bladder stones have been widely adopted to reduce the risk of complications and shorten hospital stay and convalescence. Bladder stones can be treated with open, laparoscopic, robotic-assisted laparoscopic, endoscopic (transurethral or percutaneous) surgery or ESWL [736].

6.4.3.1 Suprapubic cystolithotomy

Open suprapubic cystolithotomy is very effective but is associated with a need for catheterisation and longer hospital stay in both adults and children compared to all other stone removal modalities [736]. In children, a non-randomised study found that, if the bladder was closed meticulously in two layers, “tubeless” (drain-less and catheter-less) cystolithotomy was associated with a significantly shorter length of hospital stay compared with traditional cystolithotomy, without significant differences regarding late or intra-operative complications provided that children with prior UTI, recurrent stones, or with previous surgery for anorectal malformation (or other relevant surgery) were excluded [737].

6.4.3.2 Transurethral cystolithotripsy

In both adults and children, transurethral cystolithotripsy provides high SFRs and appears to be safe, with a very low risk of unplanned procedures and major post-operative and late complications [736].

6.4.3.2.1 Transurethral cystolithotripsy in adults

In adults, a meta-analysis of four RCTs including 409 patients demonstrated that transurethral cystolithotripsy has a shorter hospital stay and convalescence with less pain, but equivalent SFR and complications compared to percutaneous cystolithotripsy [736]. Transurethral cystolithotripsy with a nephroscope was quicker than percutaneous cystolithotripsy in three RCTs, although transurethral cystolithotripsy with a cystoscope was slower than percutaneous cystolithotripsy [736].

Rates of urethral strictures following transurethral procedures were not robustly reported: studies report rates between 2.9% and 19.6% during a follow up period of 12 – 24 months [720, 736, 738].

One small RCT demonstrated a shorter duration of catheterisation, hospital stay and procedure with transurethral cystolithotripsy than open cystolithotomy with similar SFR [736]. Meta-analysis of five RCTs found significantly shorter procedure duration for transurethral cystolithotripsy using a nephroscope vs. cystoscope with similar SFRs, hospital stay, convalescence, pain, and complications [739]. Two retrospective studies (n=188) reported that using a resectoscope or nephroscope was associated with a shorter procedure duration ($p < 0.05$) than a cystoscope for transurethral cystolithotripsy [740, 741]. This suggests that transurethral cystolithotripsy is quicker when using a continuous flow instrument.

6.4.3.2.1.1 Lithotripsy modalities used during transurethral cystolithotripsy in adults.
When considering lithotripsy modalities for transurethral cystolithotripsy, the Panel's systematic review found very low-quality evidence from five non-randomised studies (n=385) which found no difference in SFR between modalities (mechanical, laser, pneumatic, ultrasonic, electrohydraulic lithotripsy [EHL] or washout alone) [736]. Unplanned procedures and major postoperative complications were low-rate events and were not significantly different between lithotripsy modalities, although one non-randomised study (NRS) suggested these might be higher with EHL or mechanical lithotripsy than pneumatic or ultrasonic lithotripsy [742]. All outcomes had very low-quality evidence (GRADE) [736]. High-powered lasers seem to reduce lithotripsy time. Laser lithotripsy was faster than pneumatic lithotripsy (MD 16.6 minutes; CI: 23.51-9.69, p < 0.0001) in one NRS (n=62); however, a laser was used with a resectoscope and the pneumatic device with a cystoscope [743]. The same conclusion was stated in a meta-analysis of ten RCTs with high heterogeneity and small sample sizes in some of the included RCTs [744]. Continuous vs. intermittent irrigating instruments may affect the operation time more significantly than the choice of lithotripsy device [736].

6.4.3.2.1.2 Transurethral cystolithotripsy in children
In children, three NRS suggest that transurethral cystolithotripsy has a shorter hospital stay and catheterisation time than open cystolithotomy, but similar stone-free and complication rates [745]. One small quasi-RCT found a shorter procedure time using laser vs. pneumatic lithotripsy for < 1.5 cm bladder stones with no difference in SFR or other outcomes [746]. Another RCT (n=73) found shorter procedure time using pneumatic vs. laser therapy for bladder stones ≤ 1.5 cm with similar SFRs and higher (minor) complication rates for pneumatic lithotripsy [747].

6.4.3.3 Percutaneous cystolithotripsy
6.4.3.3.1 Percutaneous cystolithotripsy in adults:
One NRS found a shorter duration of procedure and catheterisation and less blood loss for percutaneous, compared with open surgery in adult male patients with urethral strictures; all patients in both groups were rendered stone-free [722].

Meta-analysis of four RCTs comparing transurethral and percutaneous cystolithotripsy found a shorter hospital stay for transurethral cystolithotripsy over percutaneous surgery. Transurethral cystolithotripsy was quicker when using a nephroscope. There were no significant differences in SFRs, major postoperative complications, or re-treatment [736].

6.4.3.3.2 Percutaneous cystolithotripsy in children:
In children, three NRS suggest that percutaneous cystolithotripsy has a shorter hospital stay and catheterisation time, but a longer procedure duration and more peri-operative complications than open cystolithotripsy; SFRs were similar [726, 736, 745, 748].

A systematic review identified four non-randomised studies comparing percutaneous and transurethral cystolithotripsy and found similar SFRs, but that transurethral surgery offers shorter duration of catheterisation and hospital stay [726, 745] in contrast, a transurethral approach may need a longer operative time and shows a higher post-operative stricture rate [748]. One small NRS found a non-significant increased risk of unplanned procedures (within 30 days of primary procedure) and major postoperative complications for percutaneous operations compared with transurethral procedures; however, age and stone size determined which intervention children underwent and all patients were rendered stone-free [726]. One RCT compared 48 boys < 14 years undergoing transurethral lithotripsy vs. 49 boys undergoing percutaneous lithotripsy with comparable success and complication rates; however, PCCL had a shorter operative time and less need for stone disintegration [749].

6.4.3.4 Extracorporeal shock wave lithotripsy
Extracorporeal SWL is the least invasive therapeutic procedure [736].

6.4.3.4.1 Shock wave lithotripsy in adults
In adults, one RCT compared SWL with transurethral cystolithotripsy in 100 patients with ≤ 2 cm bladder stones presenting with acute urinary retention. Stone-free rate after one SWL session favoured transurethral cystolithotripsy (86% vs. 98%, p = 0.03); however, following up to three sessions of SWL, there was no significant difference in SFR (94% vs. 98%, p = 0.3) [736, 750].

Two NRS compared transurethral cystolithotripsy vs. SWL and found no significant difference in SFR (97.0% vs. 93.9%, p=0.99, 97.7% vs. 89.7% p=0.07) despite larger stones in transurethral cystolithotripsy patients (4.2 vs. 2.5 cm, p=0.014; and 3.6 vs. 2.6 cm [p value not reported]) [751, 752].

Length of hospital stay appeared to favour SWL in all three studies (0 vs. 1 day, 4.8 vs. 0 days, p=0.02, 0.8 vs. 2.4 days, respectively) [750-752]. No significant differences in major post-operative or intra-operative complications were reported in any study [750-752].

One NRS compared SWL vs. open cystolithotomy in just 43 patients. Stone sizes were not comparable (2.5 vs. 7.4 cm, p < 0.001). Stone-free rates were not significantly different (93.9% vs. 100%, p=0.50). Length of stay favored SWL. There was no significant difference in intra-operative or major post-operative complications [751].

6.4.3.4.2 Shock wave lithotripsy in children

One large NRS found lower SFR for SWL than both transurethral cystolithotripsy and open cystolithotomy, despite treating smaller stones with SWL. However, the length of hospital stays favoured SWL over open cystolithotomy, although this appeared to be comparable between SWL and transurethral cystolithotripsy [753].

6.4.3.5 Laparoscopic cystolithotomy

Laparoscopic cystolithotomy has been described in adults and is typically performed in combination with simple prostatectomy using either traditional laparoscopy or with robotic assistance [754, 755]. A SR found no studies comparing laparoscopic surgery with other procedures [736].

6.4.4 Treatment for bladder stones secondary to bladder outlet obstruction in adult men

Bladder stones in men aged over 40 years may be caused by BPO, the management of which should also be considered. Bladder stones were traditionally an indication for a surgical intervention for BPO: a doctrine that has been questioned by studies. One prospective study reports urodynamics (cystometrogram) findings in 46 men aged > 60 years before and after bladder stone treatment [711]. Only 51% of men had BOO while 10% had detrusor under-activity. Eighteen percent of men had a completely normal urodynamic study and 68% had detrusor over-activity. There was no significant difference between pre- and post-bladder stone removal urodynamic findings [711].

One NRS compared 64 men undergoing transurethral cystolithotripsy with either transurethral resection of the prostate (TURP) or medical management for BPO (α-blocker with or without 5-alpha reductase inhibitor). After 28 months of follow-up, no men on medication had had a recurrence, but 34% underwent TURP: a high post-void residual urine volume predicted the need for subsequent TURP [756]. Another observational study of 23 men undergoing cystolithotripsy and commencing medical management for BPO found 22% developed a BPO-related complication, including 17% who had recurrent stones [733]. One RCT comparing cystolithotripsy with concomitant TURP to cystolithotripsy with medical management of bladder outlet obstruction with Tamsulosin and finasteride demonstrated that both groups had a significantly improved QMax, IPSS, and PVR at follow-up, although the TURP group had a longer procedure and catheterisation time [757]. Large prostates and a high PVR (> 190 ml) were predictive of needing a TURP over time in the medical management cohort, although this was based on only a small number of patients.

Large studies support the safety of performing BPO and bladder stone procedures during the same operation with no difference in major complications compared to a BPO procedure alone [758-760]. An observational study on 2,271 patients undergoing TURP found no difference in complications except UTIs, which occurred slightly more frequently in patients with simultaneously treated bladder stones: 0% vs. 0.6%, p=0.044 [758]. An observational study of 321 men undergoing Holmium laser enucleation of the prostate (HoLEP) found a higher rate of early post-operative incontinence (26.8% vs. 12.5%, p=0.03) in men having concomitant transurethral cystolithotripsy, but no difference in long-term continence rates [760]. Another larger multicenter observational study of 963 patients undergoing HoLEP found no significant differences in the frequency of complications in patients with (n=54 [5.6%]) or without concomitant transurethral cystolithotripsy [761].

6.4.5 Special situations

6.4.5.1 Neurogenic bladder and stone formation

A study of 2,825 spinal cord injury patients over eight years found a 3.3% incidence of bladder stones: 2% with CISC, 6.6% with an indwelling urethral catheter, 11% with a suprapubic catheter, and 1.1% in patients voiding using reflex micturition [766]. However, another study of 457 spinal cord injury patients for six months found no difference in bladder stones between urethral and suprapubic catheterisation [765]. Spinal cord injury patients with an indwelling urethral catheter are six times more likely to develop bladder stones than patients with normal micturition [764, 766].

The risk of stone recurrence after complete removal in spinal cord injury patients is 16% per year [765]. An RCT of 78 spinal cord injury patients who perform CISC found a significant reduction in bladder stone formation when twice weekly manual bladder irrigations were performed for six months (49% vs. 0%, p = < 0.0001), as well as less symptomatic UTIs (41% vs. 8%; p = 0.001) [767]. However, this study excluded patients who developed autonomic dysreflexia during bladder irrigations. The irrigation volume used was not reported.

6.4.5.2 Bladder Augmentation

The incidence of vesical calculus formation after bladder augmentation is 2-44% in adults [768-777], and 4-53% in children [777-791]. Following cystoplasty, stones form after 24-31 months in adults [769, 771, 776], and after 25-68 months in children [782, 785, 786, 790, 792-794]. The reported cumulative incidence of bladder stone formation after ten years is 28-36% and after twenty years is 41% [777, 795].

Risk factors for bladder stone formation after augmentation include excess mucus production, incomplete bladder emptying, non-compliance with CIC or bladder irrigations, bacteriuria or urinary tract infections (due to urease-producing bacteria), foreign bodies (including staples, mesh, non-absorbable sutures), drainage by vesico-entero-cystostomy (Mitrofanoff or Monti) [435, 769, 772, 774, 775, 782, 786, 789, 795] and voiding by CISC compared with those voiding spontaneously [773]. Gastric segment augmentation confers a lower risk of bladder stones than ileal or colonic segment cystoplasty [778, 782, 786, 789].

In previous stone formers, the rate of recurrence is 15-44% in adults [769-771, 773, 776], and 19-56% in children [435, 777, 778, 782, 784-787, 789, 794]. The risk of recurrence is greatest during the first two years, at about 12% per patient per year, with the risk decreasing with time [794].

Daily, or three-times-weekly bladder irrigations reduce the incidence of bladder stones following bladder augmentation or continent urinary diversion [435, 772]. A randomised study found that daily bladder irrigation with 240 mL of saline reduced stone recurrences (p< 0.0002, p=0.0152) and symptomatic UTIs (p < 0.0001, p < 0.0001) compared to 60mL or 120mL [772]. The frequency of bladder irrigations required is unclear.

6.4.5.3 Urinary diversion

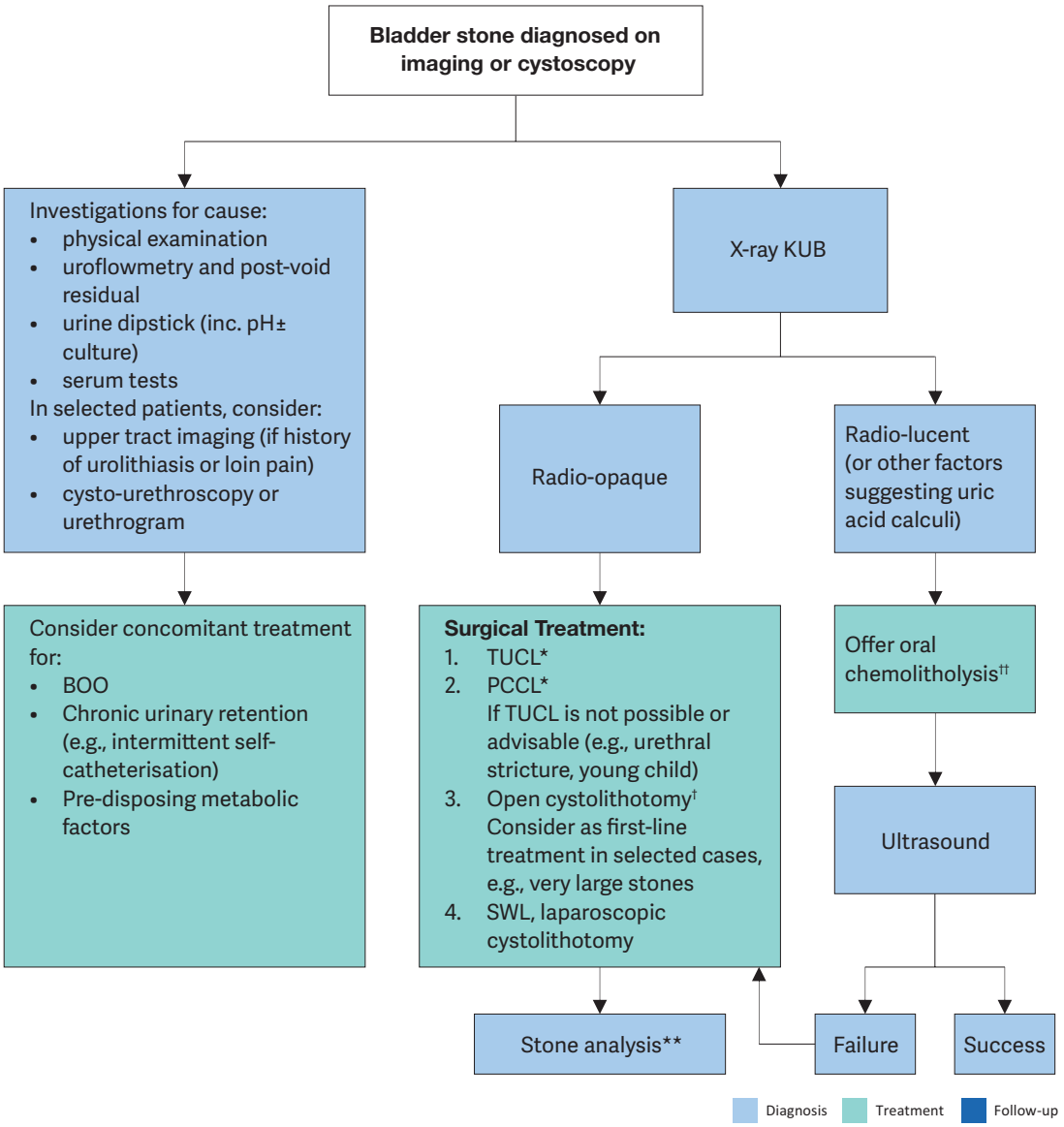
The incidence of stone formation after urinary diversion with an ileal or colon conduit is 0-3% [796, 797]. The incidence of stone formation is 0-34% in orthotopic ileal neobladders (Hautmann, hemi-Kock, Studer, T-pouch or w-neobladder) [433, 773, 797-805], and 4-6% in orthotopic sigmoid neobladders (Reddy) [802, 806]. The risk of pouch stone formation is 4-43% in adults with an ileocaecal continent cutaneous urinary diversion (Indiana, modified Indiana, Kock, or Mainz I) [425, 773, 796, 797, 805, 807]. The average interval from construction of the urinary diversion to stone detection is 71-99 months [801, 808]. In children, the incidence of neobladder stone formation is 30% after Mainz II diversion (rectosigmoid reservoir) [779], and 27% after Kock ileal reservoir construction [791].

6.4.5.4 Treatment of stones in patients with bladder augmentation or urinary diversion

Stones may be removed by open or endoscopic surgery in patients with bladder augmentation or diversion [784]. However, often access cannot be obtained through a continent vesico-entero-cystostomy without damaging the continence apparatus; hence a percutaneous or open approach is typically preferred [784].

No studies comparing outcomes following procedures for stones in reconstructed or augmented bladders were found. Two observational studies indicate that percutaneous lithotomy can be safely performed with US or CT guidance in patients with reconstructed or augmented bladders [809, 810] and is proposed to offer similar advantages over open surgery to those for percutaneous native bladder surgery. Stone recurrence after successful removal has been reported to be 10-42% [809, 810], but appears to be unrelated to the modality used for stone removal [776, 782, 786, 787, 789, 794].

Figure 6.1 Management of Bladder stones



** Lithotripsy modality at surgeon's discretion (e.g., mechanical, laser, pneumatic, ultrasonic).*
† Prefer "tubeless" procedure (without placing a catheter or drain) for children with primary bladder stones and no prior infection, surgery, or bladder dysfunction where open cystolithotomy is indicated.
*** Stone analysis should be sent for all first-time stone formers and in patients who develop a recurrence under pharmacological prevention, early recurrence after interventional therapy with complete stone clearance or late recurrence after a prolonged stone-free period (see main Urolithiasis guideline).*
†† Use an alkaline citrate or sodium bicarbonate with frequent urine pH monitoring and dose titration to achieve a consistent pH > 6.5.

BOO = Bladder Outlet Obstruction, TUCL = Trans-urethral cystolithotripsy, PCCL = Percutaneous cystolithotripsy, SWL = Shock-wave Lithotripsy.

6.5 Bladder stones follow-up

There are no studies examining the merits of differing follow-up modalities or frequencies following conservative, medical, or operative treatment of bladder stones in adults or children. Identification and prevention of the cause of bladder stone formation will be crucial to prevent recurrence (see section 6.3.2 Diagnosing the cause of bladder stones).

In adults, there is a paucity of evidence on dietary modification or medical treatment for the prevention of bladder stone recurrence. Recommendations in the EAU Guideline on Urolithiasis, based on evidence from upper tract stones, constitute the best available recommendations, especially for migratory bladder stones (see Section 4 Metabolic Evaluation and Recurrence Prevention).

Where it is possible to address the cause of secondary bladder stones (e.g., treatment of BPO), it is unclear whether metabolic intervention would offer any significant additional benefit in preventing stone recurrence. However, especially where the secondary cause cannot be addressed (e.g., indwelling catheter, neuropathic bladder, bladder augmentation, or urinary diversion); metabolic interventions are likely to reduce bladder stone recurrence rates.

Regular bladder irrigation reduces the chances of bladder stone recurrence in adults and children with bladder augmentation or continent cutaneous urinary diversion and adults with spinal cord injury who perform CISC (see section 6.4.5 Special Situations) [767, 772, 797].

In children with primary (endemic) bladder stones maintenance of hydration, avoidance of diarrhoea, and a mixed cereal diet with milk and Vitamins A and B supplements, with the addition of eggs, meat, and boiled cows' milk after one year of age are recommended to prevent a recurrence [723].

Finally, there are contradictory reports on a possible association between bladder calculi and the future development of bladder cancer [811-813]. The need for follow-up with regular cystoscopy therefore remains controversial.

6.6 Summary of evidence and recommendations for the treatment of bladder stones

Summary of evidence	LE
The incidence of bladder stones peaks at three years in children (endemic/primary stones in developing countries) and 60 years in adults.	2c
In adults, BOO is the most common pre-disposing factor for bladder stone formation.	2c
Of men undergoing surgery for BPO, 3-4.7% form bladder stones.	2b
Primary (endemic) bladder stones typically occur in children in areas with poor hydration, recurrent diarrhoea, and a diet deficient in animal protein. The following measures are proposed to reduce their incidence: maintenance of hydration, avoidance of diarrhoea, and a mixed cereal diet with milk and Vitamins A and B supplements; with the addition of eggs, meat, and boiled cows' milk after one year of age.	5
Endoscopic bladder stone treatments (trans-urethral or percutaneous) are associated with comparable SFRs, but a shorter length of hospital stay, duration of procedure and duration of catheterisation compared to open cystolithotomy in adults.	1a
Stone-free rates are lower in patients treated with SWL than those treated with open or endoscopic procedures in both adults and children.	2a
Transurethral cystolithotripsy is associated with a shorter length of hospital stay, less pain and a shorter convalescence period than percutaneous cystolithotripsy in adults.	1b
Transurethral cystolithotripsy with a nephroscope is quicker than when using a cystoscope with no difference in SFR in adults.	1a
Mechanical, pneumatic and laser appear equivalent lithotripsy modalities for use in endoscopic bladder stone treatments in adults and children.	2a
Open cystolithotomy without a retropubic drain or urethral catheter ("tubeless") is associated with a shorter length of hospital stay than traditional cystolithotomy and can be performed safely in children with primary stones and no prior bladder surgery or infections.	2b
Bladder stone removal with concomitant treatment for BOO is associated with no significant difference in major post-operative complications when compared to BOO treatment alone in adults. However, concomitant bladder stone treatment does increase the rates of short-term post-operative incontinence and UTI.	2b
The incidence of bladder stone formation in spinal cord injury patients is 19-67% over time. The absolute annual risk of stone formation in spinal cord injury patients is significantly higher with an indwelling catheter compared to those voiding with CISC or spontaneously.	2b

The incidence of bladder stone formation after bladder augmentation or vesico-entero-cystostomy is between 2-53% in adults and children.	2b
The risk of bladder stone formation in spinal cord injury, bladder augmentation or continent urinary diversion patients is reduced by performing regular bladder irrigation.	2b

Recommendations	**Strength rating**
Use ultrasound (US) as first-line imaging with symptoms suggestive of a bladder stone.	Strong
Use cystoscopy or computed tomography (CT), or kidney-ureter-bladder X-Ray (KUB) to investigate adults with persistent symptoms suggestive of a bladder stone if US is negative.	Strong
All patients with bladder stones should be examined and investigated for the cause of bladder stone formation, including: • uroflowmetry and post-void residual; • urine dipstick, pH, ± culture; • metabolic assessment and stone analysis (see sections 3.3.2.3 and 4.1 of the Urolithiasis guidelines for further details). In selected patients, consider: • upper tract imaging (in patients with a history of urolithiasis or loin pain); • cysto-urethroscopy or urethrogram.	Weak
Offer oral chemolitholysis for radiolucent or known uric acid bladder stones in adults.	Weak
Offer adults with bladder stones transurethral cystolithotripsy where possible.	Strong
Perform transurethral cystolithotripsy with a continuous flow instrument in adults (e.g., nephroscope or resectoscope) where possible.	Weak
Offer adults percutaneous cystolithotripsy where transurethral cystolithotripsy is not possible or advisable.	Strong
Suggest open cystolithotomy as an option for very large bladder stones in adults and children.	Weak
Offer children with bladder stones transurethral cystolithotripsy where possible.	Weak
Offer children percutaneous cystolithotripsy where transurethral cystolithotripsy is not possible or is associated with a high risk of urethral stricture (e.g., young children, previous urethral reconstruction, and spinal cord injury).	Weak
Open, laparoscopic, and extracorporeal shock wave lithotripsy are alternative treatments where endoscopic treatment is not advisable in adults and children.	Weak
Prefer “tubeless” procedure (without placing a catheter or drain) for children with primary bladder stones and no prior infection, surgery, or bladder dysfunction where open cystolithotomy is indicated.	Weak
Individualise imaging follow up for each patient as there is a paucity of evidence. Factors affecting follow up will include: • whether the underlying functional predisposition to stone formation can be treated (e.g., TURP); • metabolic risk.	Weak
Recommend regular irrigation therapy with saline solution to adults and children with bladder augmentation, continent cutaneous urinary reservoir or neuropathic bladder dysfunction, and no history of autonomic dysreflexia, to reduce the risk of stone recurrence.	Weak

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8. CONFLICT OF INTEREST

All members of the Urolithiasis Guidelines Panel have provided disclosure statements of all relationships that they have that might be perceived as a potential source of a conflict of interest. This information is publicly accessible through the European Association of Urology website: http://www.uroweb.org/guidelines/. 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.

9. CITATION INFORMATION

The format in which to cite the EAU Guidelines will vary depending on the style guide of the journal in which the citation appears. Accordingly, the number of authors or whether, for instance, to include the publisher, location, or an ISBN number may vary.

The compilation of the complete Guidelines should be referenced as:
EAU Guidelines. Edn. presented at the EAU Annual Congress Paris 2024. ISBN 978-94-92671-23-3.

If a publisher and/or location is required, include:
EAU Guidelines Office, Arnhem, the Netherlands. http://uroweb.org/guidelines/compilations-of-all-guidelines/

References to individual guidelines should be structured in the following way:
Contributors' names. Title of resource. Publication type. ISBN. Publisher and publisher location, year.

EAU Guidelines on Urethral Strictures

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1. INTRODUCTION

1.1 Aims and scope

The European Association of Urology (EAU) Urethral Strictures Guidelines aim to provide a comprehensive overview of urethral strictures in male, female, and transgender patients. The Panel is aware of the geographical variations in healthcare provision.

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

1.2 Panel composition

The EAU Urethral Strictures Guidelines panel consists of an international multidisciplinary 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: http://www.uroweb.org/guideline/urethral-strictures/.

1.3 Available publications

Alongside the full text version, a quick reference document (Pocket Guidelines) is available in print and as an app for iOS and Android devices. These are abridged versions which may require consultation together with the full text version. All documents can be viewed through the EAU website: http://www.uroweb.org/ guideline/urethral-strictures/. A list of supplementary tables supporting this text can also be found online, along with an appendix of abbreviations specific to this text: https://uroweb.org/guideline/urethralstrictures/?type=appendices-publications.

1.4 Publication history

This Guideline was first published in 2021. 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. METHODOLOGY

2.1 Methods

For the 2021 Urethral Strictures Guidelines, new and relevant evidence was identified, collated, and appraised through a structured assessment of the literature. A broad and comprehensive literature search, covering all sections of the Guidelines was performed. Databases searched included Medline, EMBASE, and the Cochrane Libraries, covering a time frame between 2008 and 2019 and restricted to English language publications. The panel defined by consensus inclusion and exclusion criteria for each topic before the scope search. Detailed search strategies are available online: https://uroweb.org/guideline/urethral-strictures/.

Recommendation within the Guidelines are developed by the panels to prioritise clinically important care decisions. The strength of each recommendation is determined by the balance between desirable and undesirable consequences of alternative management strategies, the quality of the evidence (including certainty of estimates), and the nature and variability of patient values and preferences [1, 2]. This decision process, which can be reviewed in the strength rating forms which accompany each guideline statement, addresses a number of key elements:

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

Strong recommendations typically indicate a high degree of evidence quality and/or a favourable balance of benefit to harm and patient preference. Weak recommendations typically indicate availability of lower quality evidence, and/or equivocal balance between benefit and harm, and uncertainty or variability of patient preference [4].

The Panel wants to highlight that "success" in urethral stricture treatment is poorly defined and subjective. "Success" is usually defined as urethral patency, either subjective by the absence of voiding symptoms or objective by imaging or urethral calibration. Despite urethral patency, the patient themselves might not consider the treatment as successful because of functional consequences (e.g., post-void dribbling, erectile/ejaculatory dysfunction, altered genital appearance). In this Guideline, the Panel agreed to avoid the term "success". Instead, the term "patency rate" or "stricture recurrence rate" will be used to clarify that only stricture recurrence was taken into consideration (as assessed by the authors).

The Panel would like to stress that patency after urethral surgery is dependent on the general principles of wound healing. These principles have stood the test of time and need to be respected [5]. Some examples:

- An anastomosis should be made between healthy urethral ends and without any tension.
- A graft requires a well-vascularised graft bed with a close contact between the graft and graft bed to promote imbibition and inosculation.
- If the full circumference of the urethral mucosa is destroyed, spontaneous regeneration will not take place.
- Contraction and fibrosis in a wound only stops after it is covered by its epithelium.

The Panel conducted two systematic reviews (SR) to support guideline recommendations, which were published in 2021:

- What is the role of single-stage oral mucosa graft urethroplasty in the surgical management of Lichen Sclerosus-related stricture disease in men? A systematic review [6];
- Free Graft Augmentation Urethroplasty for Bulbar Urethral Strictures: Which Technique Is Best? A Systematic Review [7].

The results of these reviews are included in the 2023 Urethral stricture guidelines.

In addition, the panel drafted three summary papers of the guidelines which were published in European Urology and European Urology Focus:

- EAU guidelines on urethral stricture disease (part 1): management of male urethral stricture disease [8];
- EAU Guidelines on urethral stricture disease (part 2): diagnosis, perioperative management, and follow-up in males [9];
- EAU guidelines on urethral stricture disease (part 3): management of strictures in females and transgender patients [10].

2.2 Review

The Urethral Strictures Guidelines were peer reviewed prior to initial publication in 2021.

3. DEFINITION, EPIDEMIOLOGY, AETIOLOGY AND PREVENTION

3.1 Definitions

In males, a urethral stricture refers to a narrowed segment of the anterior urethra due to a process of fibrosis and cicatrisation of the urethral mucosa and surrounding spongiosus tissue ("spongiofibrosis") [11, 12]. In the male posterior urethra, there is no spongiosus tissue and at this location the terms stenosis is preferred [11, 12]. The definition of meatal stenosis is generally accepted as a short distal narrowing at the meatus, without involvement of the fossa navicularis [12].

There is no universal definition for what constitutes a female urethral stricture (FUS). Female urethral stricture is defined by most authors as a 'fixed anatomical narrowing' causing reduced urethral calibre [13, 14]. This reduced urethral calibre is variously defined as between < 10 Fr to < 20 Fr [15, 16] with the majority of series defining < 14 Fr as diagnostic, compared with a 'normal' urethral calibre of 18-30 Fr.

In transgender patients, the term stricture is also used to define a narrowing of the reconstructed urethra despite the absence of surrounding spongious tissue.

3.2 Epidemiology

In males, a sharp increase in incidence is observed after the age of 55 years, with a mean age of 45.1 [17, 18]. Overall, the incidence is estimated to be 229-627 per 100,000 males [17]. The anterior urethra is most frequently affected (92.2%), in particular the bulbar urethra (46.9%) [18].

In females, 2-29% of patients presenting with refractory lower urinary tract symptoms (LUTS) have bladder outflow obstruction (BOO) [19-22] of whom 4-20% will have a urethral stricture [21-23]. True FUS therefore occurs in 0.08-5.4% of women with refractory LUTS. There is a markedly increased incidence in women over 64 years of age [24].

After hypospadias repair, meatal stenosis and urethral strictures are reported in 1.3-20% of cases, depending on the severity of the hypospadias and the technique used [25]. There is a significantly higher incidence of this type of strictures in well-resourced countries due to a higher surgical repair rate [26].

Up to 18% of all urethral strictures have been reported to involve the meatus or fossa navicularis, usually due to failed hypospadias repair (FHR), lichen sclerosus (LS), trauma/instrumentation or idiopathic causes [27-30]. Meatal stenosis post-circumcision has been reported in less than 0.2% of children undergoing circumcision as neonates [17].

In female-to-male (FtM) transgender patients ("transmen"), 2-56% will suffer a urethral stricture. Strictures almost exclusively arise at the neomeatus in male-to-female (MtF) transgender patients ("transwomen") and occur in 4-40% of cases [31].

3.3 Aetiology and prevention

Stricture aetiology differs significantly throughout different regions in the world, due to differences in healthcare quality and environmental and practice patterns [26]. Regardless of geography, urethral stricture disease adversely impacts physical health and quality of life (QoL) [32, 33], notwithstanding costs associated with the treatment of primary and recurrent disease [34, 35]. The rationale for preventing urethral strictures is to avoid morbidity to the individual and costs to society. Prevention of urethral strictures encompasses reducing the causes of stricture (e.g., infection, trauma, iatrogenic injury) and where this is not possible, mitigating the risk.

*3.3.1 **Aetiology and prevention in males***

a. Sexually transmitted infection

Urethritis due to sexually transmitted infection (STI), in particular gonorrhoea, was previously a major cause of urethral strictures in well-resourced countries accounting for 40% of all cases [36]. The wide-scale promotion of safe sexual practices and easier access to sexual health services, resulting in timely treatment with antimicrobials, is thought to have led to the considerable reduction in the problem [36]. Infective urethritis now accounts for 0.9% to 4.6% of cases in contemporary series from well-resourced countries [36, 37] but continues to be the major cause of strictures in low-resourced countries comprising 41.6% of all strictures [38].

Summary of evidence	**LE**
Access to investigation and treatment of STI is associated with a temporal decline in the incidence of infective urethritis related strictures.	3

Recommendation	**Strength rating**
Advise safe sexual practices, recognise symptoms of sexually transmitted infection, and provide access to prompt investigation and treatment for men with urethritis.	Strong

b. Inflammation

Lichen sclerosus involves the urethra in 20% of cases [39] and is the most common cause of panurethral stricture disease (48.6%) [18]. The aetiology of LS has not been fully elucidated but is thought to have an autoimmune origin [40]. Lichen sclerosus may be associated with environmental factors and non-autoimmune comorbidities. Uncircumcised men are far more likely to suffer LS than circumcised men (age-adjusted odds ratio [OR] of 53.55; 95% confidence interval [CI]: 7.24-395.88) [41]. Lichen sclerosus is also associated with higher mean body mass index (BMI), diabetes mellitus, coronary artery disease, tobacco usage, hyperlipidaemia, and hypertension [42-44].

c. External urethral trauma

External trauma to the urethra is the second most common cause of stricture formation in adults [36]. The urethra is vulnerable to trauma during certain activities including sport, driving a vehicle, sexual intercourse and during combat. The bulbar urethra is the site most frequently affected by blunt trauma [12], usually as a result of straddle injuries or kicks to the perineum. Penile fracture is associated with a urethral injury in 15% of cases [45]. Motor vehicle accidents are the main cause of blunt injuries to the posterior urethra associated with pelvic fractures [46]. Penetrating injuries of the urethra are uncommon during non-combat situations [47].

d. Iatrogenic urethral injury

Iatrogenic injury to the urethra is one of the most common causes of strictures in well-resourced countries [18, 36] accounting for 32-79% of all strictures [36, 48]. Preventing iatrogenic urethral injury represents the main way in which urologists can prevent urethral strictures. Iatrogenic urethral injury most commonly results from urethral instrumentation (e.g., catheterisation, cystoscopy), surgery for benign prostatic obstruction (BPO), surgery for prostate cancer, or radiotherapy [37].

d.1 Urethral catheterisation

Urethral strictures are a recognised complication of urethral catheterisation accounting for 11.2-16.3% of all strictures [18, 36]. In a meta-analysis by Hollingsworth *et al.*, the pooled percentage of patients who developed urethral stricture or erosion after short-term catheterisation (< 3 weeks) in higher-quality studies was 3.4% (CI: 1-7%) [49]. In studies comprised mainly of men with spinal cord injury with indwelling urethral catheters, the pooled estimate of urethral stricture or erosion was 8.7% (CI: 0.0-18.7%) [49].

Urethral strictures following catheterisation may arise as a consequence of injury during attempts at insertion or during the period a catheter remains *in situ*. During insertion, the urethra may be injured by formation of a false passage by the catheter tip (29.7%) or inflation of the balloon within its lumen (70.3%) [50]. The rate of urethral injuries due to catheterisation was found to be 3.2 per 1,000 inpatients [51]. A six-month prospective multicentre study found that of 37 patients with catheter-related urethral trauma referred to urologists, 24% continued to perform ISD once weekly and 11% required at least one urethral dilation for urethral stricture [52]. In another follow-up study of 37 patients with catheter-related urethral trauma, 78% of patients developed urethral stricture [50]. The most common locations of trauma are the bulbar and posterior urethra [53].

Catheter-related trauma can be prevented through several measures [54]. Studies have indicated around 25% of all indwelling catheterisations in hospitals were unnecessary and inappropriate [55, 56]. Implementation of guidelines [57, 58] and specific criteria [59] have been shown to reduce catheterisation rates. Several studies have identified deficits in the knowledge of urethral catheterisation amongst resident doctors [60, 61]. This is postulated to be a factor in catheter-related trauma [61]. A targeted training program on urethral catheterisation for nursing staff was shown to be effective in reducing iatrogenic urethral injuries in a prospective single institution study [62].

In addition to guidance and education, another approach to safer catheterisation is modification of the standard Foley catheter. A novel catheter balloon pressure valve safety system was developed to prevent balloon inflation injury though this has not been assessed in comparative studies [63, 64]. Bugeja *et al.*, studied the use of urethral catheterisation device (UCD) incorporating a guidewire, in prospective observational cohort study that included 174 patients. The incidence of adverse events was 7% with standard Foley catheterisation vs. 0% with the UCD (no statistical analysis was performed) [65]. A further prospective observational study found that Seldinger technique catheterisation could be used successfully by non-urology trained doctors [66]. These technologies need to be further assessed in prospective raondomised controlled trials (RCTs), incorporating cost-benefit analysis.

Catheter diameter is suggested as a possible contributing factor to urethral stricture due to a pressure effect on the urethral wall [67]. Decreasing the catheter size from 22 Fr to 18 Fr significantly decreased the risk of fossa navicularis strictures (6.9% vs. 0.9%, p=0.02) after radical prostatectomy (RP) [68]. Catheter material may also have an influence on the occurrence of stricture. In the 1970s/80s several comparative studies in patients undergoing cardiac surgery demonstrated that non-coated latex catheters were associated with a greater incidence of urethritis and more stricture formation than silicone catheters [69-71]. Other studies showed no difference [72-74]. Modern latex catheters have polymeric coatings [75] due to the concern with regards to stricture alongside the risk of hypersensitivity and the demonstrable *in vitro* toxicity of latex. Prolonged urethral catheterisation has also been implicated in the aetiology of stricture (e.g., poly-trauma, burns patients) [48].

Summary of evidence	LE
A significant proportion of catheter insertions in hospitalised patients were considered unnecessary.	2b
Education programs can reduce the incidence of catheter-related urethral injury.	2a
Larger catheter size was associated with a greater risk of navicular fossa strictures.	3
Non-coated latex catheters are associated with a greater degree of urethritis and possibly a greater risk of urethral strictures than non-latex catheters or coated latex catheters.	1a

Recommendations	Strength rating
Avoid unnecessary urethral catheterisation.	Strong
Implement training programmes for physicians and nurses performing urinary catheterisation.	Strong
Do not use catheters larger than 18 Fr if urinary drainage is the only purpose.	Weak
Avoid using non-coated latex catheters.	Strong

d.2 Transurethral prostate surgery

Urethral stricture following transurethral prostate surgery occurs in between 4.5-13% of patients [76], whereas bladder neck stenosis (BNS) occurs in between 0.3-9.7% [77]. Transurethral surgery is the most common cause of iatrogenic urethral stricture accounting for 41% of all causes [48]. The most common location for urethral stricture is the bulbomembranous urethra, followed by the fossa navicularis and penile urethra [78, 79]. Postulated mechanisms include friction at the penoscrotal junction, lack of adequate lubrication, repetitive 'in and out' movement of the resectoscope, breach of mucosal integrity leading to urine extravasation and monopolar current leak due to inadequate resectoscope insulation [80]. Bladder neck stenosis may be related to excessive and/or circumferential resection and the use of relatively large resection loops which may generate excessive heat in small intraurethral adenomas leading to scarring [77, 81]. Stenoses of the posterior urethra may also be due to a prolonged period of post-operative inability to void [82].

d.2.1 Risk factors for development of urethral stricture and bladder neck stenosis

Several risk factors for the development of urethral stricture and BNS following transurethral prostate surgery have been identified. Both prostatic inflammation (OR: 4.31) and operative time > 60 min (OR: 4.27) were found to be independent predictors of stricture after monopolar transurethral resection of prostate (TURP) [83]. In terms of bipolar TURP, slower resection rate (OR: 0.003), intraoperative urethral mucosa rupture (OR: 2.44) and post-operative infection were shown to be independent predictors (OR: 1.49) [84, 85]. A larger-calibre endoscopic sheath (26 Fr vs. 24 Fr) was associated with a greater risk of bulbar urethral stricture following monopolar TURP (11.4% vs. 2.9%, p=0.018) [86]. Room temperature irrigation solution was associated with a greater risk of urethral stricture following combined transurethral resection and vaporisation of the prostate compared to body temperature irrigation (21.3% vs. 6.3%, p=0.002) [87].

Bladder neck stenosis is known to occur more frequently in smaller prostate glands after both monopolar and bipolar TURP [88, 89]. Lee *et al*., found that adenoma weight was an independent risk factor for BNS after monopolar TURP [89]. Meanwhile, Tao *et al.*, found total prostate volume (< 46.2 g) (OR: 1.5), but not resected gland weight, to be an independent risk factor [84].

d.2.2 Incidence of urethral stricture and bladder neck stenosis with different energy modalities

A SR and meta-analysis by Cornu *et al.*, showed no significant differences in urethral stricture and BNS rates by energy modality (monopolar, bipolar, holmium laser enucleation, photoselective vaporisation) [76]. In another meta-analysis assessing outcomes of thulium (Tm:Yag) laser and bipolar TURP, no difference in urethral stricture and BNS rates were found between the two modalities [90]. The presence of potentially confounding factors such as endoscopic sheath diameter, energy setting used, procedural length and length of follow-up make inter-study comparisons between energy modalities problematic. Overall, there is no strong evidence that any single modality is associated with a clinically significant higher incidence of urethral stricture and BNS than others. Selection of modality should be based on a comprehensive evaluation of clinical safety and efficacy. A summary of incidences of urethral stricture and BNS with different modalities is presented in Table 3.1.

A systematic review analysing different techniques used for BPH surgery, showed the lowest incidence of urethral strictures in enucleation procedures, followed by B-TURP and ablation, and M-TURP. However, after twelve months of follow-up there were no significant differences in stricture rate [91].

Table 3.1: Incidence of urethral stricture and bladder neck stenosis by transurethral modality (adapted from Chen *et al*. 2016 [77])

Modality	Urethral stricture	Bladder neck stenosis
Transurethral resection of prostate (TURP) - monopolar and bipolar	1.7 to 11.7%	2.4 to 9.7%
Holmium enucleation of the prostate (HoLEP)	1.4 to 4.4%	0 to 5.4%
Photo-selective vaporisation (PVP)	0 to 4.4%	1.4 to 3.6%

d.2.3 Interventions to prevent urethral stricture and bladder neck stenosis

Sciarra and colleagues conducted a single-blind RCT (n=96) to assess the use of rofecoxib for stricture prevention following TURP. At twelve months follow-up a urethral stricture was found in 17% and 0% of cases in the placebo and rofecoxib groups, respectively (p=0.0039) [92]. Chung *et al.*, conducted a single blinded RCT (n=180) evaluating the effect of urethral instillation of hyaluronic acid (HA) and carboxymethylcellulose (CMC). Urethral stricture on urethrography was diagnosed in 1.25% and 8.64% of patients in the treatment and placebo group respectively (p=0.031). Further RCTs are needed to confirm these findings and the safety of the pharmacological interventions.

Several earlier comparative studies assessed whether routine preliminary urethrotomy with an Otis urethrotome prevented the incidence of stricture following TURP [93-96]. Only one of these reported at least twelve month follow-up, finding no significant difference in stricture rate in patients undergoing TURP alone vs. Otis urethrotomy followed by TURP (21% vs. 14%) [97]. Others have suggested performing internal urethrotomy where there are pre-existent meatal or urethral strictures [98].

Adjunctive transurethral incision of the prostate (TUIP) at the end of TURP to reduce the rates of BNS was studied by Lee *et al*. [89]. A total of 1,135 patients of whom 667 underwent TURP and 468 underwent TURP plus TUIP were retrospectively studied. At median follow-up of 38 months, the incidence of BNS was 12.3% for the TURP group vs. 6.0% for the TURP plus TUIP group ($p < 0.001$). In glands < 30 g, the incidence of BNS in the TURP vs. the TURP plus TUIP group was 19.3% and 7.7%, respectively ($p < 0.05$). The clinical efficacy and safety of additional surgical interventions to prevent urethral stricture and BNS need to be confirmed in larger prospective RCTs before their use can be recommended.

Summary of evidence	LE
An RCT with more than twelve months follow-up failed to demonstrate a significant reduction in stricture rate using routine urethrotomy prior to TURP.	1b

Recommendation	Strength rating
Do not routinely perform urethrotomy when there is no pre-existent urethral stricture.	Strong

d.3 Radical prostatectomy

Radical prostatectomy has been associated with vesico-urethral anastomosis stricture (VUAS) in 0.5-30% of patients [77], though most modern series report it in the range of 1-3% [99]. The risk of stricture formation after salvage RP is notably higher (22-40%) [100]. Most VUAS develop within the first two years [100, 101]. A 2012 meta-analysis by Tewari *et al.*, showed no significant difference in VUAS between open-, laparoscopic and robotic RP [102]. In contrast, a more recent analysis of a national cohort in the UK found that VUAS rate after robotic RP was 3.3%, which is significantly lower than following laparoscopic (5.7%) or open RP (6.9%) [103]. These findings are consistent with an earlier similar study conducted in the USA [104]. The difference in VUAS rates may be explained by the level of experience and surgical volume of surgeons [105]. The cohort studies represent "real world" data, including all levels of surgical experience and surgical volumes whereas the meta-analysis is based on clinical studies. Thus, the better outcomes for robotic RP in the population studies may be related to the shorter learning curve [106].

d.3.1 Risk factors for development of vesicourethral anastomosis strictures

These include higher grade cancer, more advanced stage, higher prostate volume, coronary artery disease, obesity, hypertension, diabetes mellitus, previous bladder outlet surgery and older age [99, 107, 108]. Surgical factors include the use of non-nerve-sparing technique, anastomotic urine leak, increased operative time and increased estimated blood loss [99, 107, 108]. In addition, low-volume surgeons (< 40/year) were shown to have higher VUAS rates, 27.7%, compared to high-volume surgeons (> 40/year), 22% [109].

d.3.2 Interventions to prevent vesicourethral anastomosis strictures

Srougi *et al*., studied bladder neck mucosal eversion in a prospective RCT of 95 patients. No significant difference was found in rates of VUAS at twelve months follow-up [110]. A meta-analysis by Kowelewski *et al.*, comparing interrupted vs. continuous vesico-urethral anastomosis suturing found no difference in VUAS rates [111]. Another SR by Bai *et al*., compared barbed sutures to conventional sutures, and although heterogeneity across studies precluded meta-analysis, no patients developed VUAS with either approach [112].

d.4 Prostate radiation and ablative treatments

Urethral strictures occur in 1.5% of patients undergoing external beam radiation therapy (EBRT), 1.9% having brachytherapy (BT) and 4.9% who receive combination EBRT-BT at around four years follow-up [113]. These strictures typically occur in the bulbomembranous urethra [114]. As opposed to RP, stricture incidence after irradiation increases with time [100, 113]. For the ablative treatments, the stricture incidence after cryotherapy and high-intensity focused ultrasound (HIFU) is 1.1-3.3% and 10.3%, respectively [100, 115]. The use of these modalities in the salvage setting is associated with increased risk of stricture formation: 3-10% after salvage EBRT, 5-12% after salvage cryotherapy and 15-30% after salvage HIFU [100]. Due to the increasing utilisation of prostate irradiation (EBRT, BT) and ablative treatments (cryotherapy, HIFU), an increasing number of respectively radiation-induced and ablative treatment-induced strictures are expected [116].

d.4.1 Risk factors for the development of radiation strictures

Awad *et al*., performed a multivariate meta-regression analysis including 46 studies, finding combining ERBT + BT and length of follow-up to be significant predictors of urethral stricture following prostate radiation [113]. Factors not shown to predict urethral stricture included biochemical equivalent dose, age, and androgen deprivation therapy [113]. Previous TURP was not included in the analysis, but has been found to be an independent predictor of stricture (HR: 2.81) in a previous multivariate analysis from a single institution [117] as well as PSA level < 10 ng/ml (HR: 0.47) [118].

d.4.2 Interventions to prevent radiation induced urethral strictures

Delaying adjuvant or salvage EBRT by nine months is associated with lower rates of urethral stricture (HR: 0.6) [119]. This has to be balanced with risk of delaying treatment in terms of cancer control [77]. In BT, it has been reported that downward movement of needle applicators occurs between fractions [120]. This may explain why strictures occur below the prostatic apex [118] in the so called "hot spot" [121]. Several measures taken together are thought to have contributed to a reduction in urethral stricture formation with BT including reduction of dose to the "hot spot", more careful needle placement, avoiding midline insertion and the introduction of plastic needles rather than steel [113].

e. Failed hypospadias repair

Although urethral strictures after hypospadias repair are sometimes considered as iatrogenic [36], they are a very specific subtype and should be considered as a separate entity. The main reasons for this are the absence of spongiosus tissue at different levels within the penile urethral segment, and the lack of high-quality local tissues for urethral reconstruction [122].

f. Congenital

The diagnosis of a congenital urethral stricture can only be made in the absence of other possible aetiology, such as iatrogenic, inflammatory, and traumatic causes [123]. Congenital strictures are thought to be consequent to incomplete or incorrect fusion of the urethra formed from the urogenital sinus with the urethra formed following closure of the urethral folds. They typically have a deep bulbar location and are usually short. In general, congenital strictures are diagnosed at a young age (Moorman's ring or Cobb's collar).

g. Idiopathic

Idiopathic strictures are seen in 34% of all penile strictures and in 63% of all bulbar strictures [124]. Unrecognised trauma is thought to be a possible aetiology of idiopathic urethral strictures [26].

3.3.2 *Aetiology in females*

The cause of FUS was idiopathic in 48.5%, iatrogenic in 24.1%, resulting from prior urethral dilations, difficult/traumatic catheterisation with subsequent fibrosis, urethral surgeries (mainly diverticulum surgery, fistula repair and anti-incontinence procedures) and trauma (mainly following pelvic fracture) in 16.4% [125-137]. Radiation therapy and infections are rare causes of FUS [138]. The most common segment of urethra affected is the midor mid-to-distal (58%). Panurethral strictures are rare (4%) [15, 125, 127, 128, 130-132, 137, 139].

For further information see online supplementary Tables S3.1 and S3.2.

4. CLASSIFICATIONS

4.1 According to stricture location

Classification according to stricture location is important as this will affect further management.

4.1.1 *In males*

4.1.1.1 *Anterior urethra*

The anterior urethra runs from the meatus to the urogenital diaphragm and is surrounded in its entire length by the corpus spongiosum [11, 140]. Further subdivision is made in three different areas (from distal to proximal) [12]:

Meatal strictures: these strictures are located at the external urethral meatus and may extend into the fossa navicularis of the glans.

Penile strictures: these are located in the segment between the fossa navicularis and the bulbar urethra. Externally, the penile urethra begins approximately at the balanopreputial sulcus and continues to the penoscrotal junction. The whole penile urethral segment lies in the groove ventral to corpora cavernosa and is surrounded by a thin layer of corpus spongiosum.

Bulbar strictures: the bulbar urethra starts at the penoscrotal junction and is surrounded by the bulbospongious muscle. It ends in the membranous urethra proximally at the level of the urogenital diaphragm. The bulbar urethra can be subdivided into a proximal and distal part. The proximal bulbar urethra is defined as the segment within 5 cm of the membranous urethra; the urethra lies eccentrically in this part with abundant ventral spongious tissue. The distal bulbar urethra is defined as the adjoining segment extending to the penoscrotal junction [141]. Strictures extending towards the membranous urethra are termed bulbomembranous strictures (BMS).

Penobulbar strictures: these extend from the penile urethra into the bulbar segment, compromising long segments of urethra.

The difference between penobulbar strictures and multifocal strictures should be noted. The latter are defined by two or more narrowed segments, either in the same or different subdivision of the urethra but preserving healthy lengths of urethra between them (e.g., iatrogenic strictures related to TUR procedures which typically affect the fossa navicularis and the penoscrotal junction with healthy urethra in between).

4.1.1.2 *Posterior urethra*

The posterior urethra is approximately 5 cm long, with three different segments [12]:

- The membranous urethra is the area of the urethra traversing the urogenital diaphragm, between the proximal bulbar and the distal verumontanum.
- The prostatic urethra runs through the prostatic gland, starting at the proximal membranous urethra and extending to the bladder neck.
- The bladder neck is surrounded by the internal urinary sphincter and is the junction between the prostatic urethra and the bladder. Stenosis (or contracture) of the bladder neck implies a prostate *in situ* (i.e., after TURP or simple prostatectomies). If the narrowing or obliteration appears at this level but after a RP, the correct term is VUAS [12].

4.1.2 *In females*

The female urethra is approximately 4 cm long and arbitrarily divided in an upper, mid, and lower part [15, 125, 127, 128, 130-132, 137, 139].

4.2 According to stricture tightness

Several classifications systems have been proposed over the years [142]. The definition of low- vs. high-grade strictures remains debatable [143-145]. A urethral plate less than 3 mm is considered a high-grade or tight stricture [146]. It has been demonstrated with a normally functioning bladder that flow rate will not diminish until the urethral lumen has a diameter below 10 Fr [144].

Table 4.1 presents a suggested classification for male patients with a normal functioning bladder. This classification was developed by the EAU Urethral Stricture Panel based on a consensus process.

Table 4.1: EAU classification according to the degree of urethral narrowing

Category	Description	Urethral lumen (French [Fr])	Degree
0	Normal urethra on imaging	-	-
1	Subclinical strictures	Urethral narrowing but ≥ 16 Fr	Low
2	Low grade strictures	11-15 Fr	
3	High grade or flow significant strictures	4-10 Fr	High
4	Nearly obliterative strictures	1-3 Fr	
5	Obliterative strictures	No urethral lumen (0 Fr)	

4.3 Strictures in transgender men and woman

*4.3.1 **Trans women***

After MtF gender confirming surgery, the penile urethra has been resected. Meatal strictures are defined as strictures occurring at the neomeatus, which is formed between the junction of the distal bulbar urethra and the neovagina. The other segments (bulbar and posterior) are the same as in a biological man.

*4.3.2 **Trans men***

Four different areas can be identified in the urethra after FtM gender confirming surgeries [147]:

- The native urethra is the female urethral segment which remains preserved during surgery. It goes from the bladder neck to the original external meatus.
- The fixed part (pars fixa) or perineal urethra follows the native urethra, starting at the original external meatus. This segment is reconstructed using local tissues, typically vestibular mucosa, or anterior vaginal mucosa. Its course is similar to the bulbar urethral segment in males, but without being covered by spongiosal tissue.
- The anastomotic part is the area where the pars fixa joins the neophallus.
- The phallic urethra is the segment located within the neophallus or the metoidioplasty and is usually made of skin tube. Its course is similar to the penile urethra in males, but without being covered by spongiosal tissue.

5. DIAGNOSTIC EVALUATION

A comprehensive diagnostic evaluation of urethral stricture disease encompasses clinical history and examination, urinalysis (+/- culture), uroflowmetry and post-void residual (PVR) assessment, radiography, and endoscopy.

5.1 Patient history

The purpose of history taking is to assess symptoms including severity and duration, possible aetiology, prior treatments, complications, associated problems, and patient factors that may impact upon surgical outcome.

The clinical presentation of urethral stricture disease is varied. In a retrospective analysis of 611 patients with an endoscopically confirmed diagnosis of urethral stricture, LUTS were the most common presentation (54.3%) followed by acute urinary retention (22.3%), urinary tract infection (UTI) (6.1%) and difficult catheterisation (4.8%) [148]. In a retrospective study of 214 patients who underwent anterior urethroplasty, weak stream was reported as the most common individual LUTS (49%) followed by incomplete emptying (27%) and urinary frequency (20%) [149]. A further retrospective series of 614 patients undergoing anterior urethroplasty found post-void dribble to be present in 73% [150].

Genitourinary pain is a common feature, affecting 22.9-71% [34, 148]. Pain may be felt in the bladder and/or urethra, is associated with more severe LUTS, is more likely to be felt by younger men and resolves in most following reconstruction [32]. Other complaints include spraying (9%), visible haematuria (3.1-5%), urethral abscess/necrotising fasciitis (2.3%), urgency (14%) and incontinence (1-4%) [148, 149].

To establish aetiology, an enquiry about a history of pelvic, genital, or perineal trauma, prior instrumentation, prior surgeries, irradiation or focal therapies and urethritis should be made. It is important to document prior surgical approaches and date of the most recent intervention (e.g., dilatation) as this may impact upon the timing of radiological evaluation or surgical treatment.

Problems of sexual function are common in patients with urethral stricture disease [151, 152] and sexual function may be impacted upon by surgical intervention [153, 154]; therefore, the status of erectile and ejaculatory function should be established and documented using validated tools.

The performance status of the patient should be determined as it may influence the choice of treatment (curative or palliative). A past medical history should assess for factors that may impact upon tissue healing including diabetes, immunosuppression, and smoking. Oral tobacco use or the chewing of betel leaves may increase the risk of morbidity at the harvest site or render oral mucosa too poor for use. Prior harvest of oral mucosa should be noted as alternative sources for tissue transfer may need to be considered [155] or alternative surgical approaches (e.g., perineal urethrostomy [PU]).

5.2 Physical examination

The abdomen should be examined for the presence of a palpable bladder. The location of any suprapubic tube should be noted to assess its potential utility for antegrade cystoscopy or the placement of a sound (to facilitate repair) [156]. Examination of the genitalia should note the presence of foreskin, the position and size of the meatus as well as any evidence of scarring suggestive of LS. Pre-operative biopsy to confirm LS may be performed if this alters management and is essential if malignancy is suspected [157].

The presence of penile or perineal fistulae should be noted. The urethra should be palpated to assess for induration suggestive of significant fibrosis. Rarely a mass may signify a urethral carcinoma. A rectal examination to assess for prostatic pathology, which may be the cause of urinary symptoms, should be undertaken. In patients with posterior urethral stenosis rectal adherence to the prostate and the mobility of the surrounding tissues should be assessed [158]. The oral cavity should be examined for the suitability of oral mucosa. Measurement of BMI will identify obese individuals who are at greater risk of leg compartment syndrome when placed in the lithotomy position for a prolonged time period [159]. Assessing hip mobility is important when considering an exaggerated lithotomy position as some patients may have limited hip flexion due to unresolved orthopaedic problems [156].

*5.2.1 **Further diagnostic evaluation***

5.2.1.1 Patient reported outcome measure (PROM)

The first validated urethral stricture surgery PROM (USS-PROM) was reported in 2011 [160]. It consists of six LUTS questions derived from the International Consultation on Incontinence Questionnaire Male LUTS (ICIQ-MLUTS) module, a LUTS-specific QoL question, the Peeling voiding chart and the EQ-5D to assess overall health-related QoL (HRQoL). The post-operative questionnaire contains an additional two questions to assess overall patient satisfaction. This PROM has been validated in several other languages (German, Spanish, Italian, Dutch, Turkish, Polish, Japanese) and is increasingly used in research studies as well as clinical practice. A further PROM is in development in North America but requires validation [161] (see section 11. Follow-up).

Summary of evidence	**LE**
A specific urethral stricture surgery patient reported outcome measure was found to have psychometric validity in the assessment of patient-derived benefit from surgical intervention for urethral stricture disease.	2a
Sexual dysfunction is prevalent in patients with urethral strictures and sexual function can be affected by surgical management of urethral stricture.	3

Recommendations	Strength rating
Use a validated patient reported outcome measure (PROM) to assess symptom severity and impact upon quality of life in men undergoing surgery for urethral stricture disease.	Strong
Use a validated tool to assess sexual function in men undergoing surgery for urethral stricture disease.	Strong

5.2.1.2 Urinalysis and urine culture

Urinalysis is an essential component of the work up of patients with LUTS. If infection is suggested, urine culture should be performed to confirm the diagnosis and identify the causative organism and sensitivity to antibiotics. Bacteriuria should be treated prior to surgical intervention to prevent peri-operative sepsis [162] (see section 10. Peri-operative care).

5.2.1.3 Uroflowmetry and post-void residual estimation

A reduced maximum flow rate with a prolonged plateau is characteristic of the constrictive obstruction caused by urethral stricture. However, interpretation of flow patterns is subjective and is not considered a reliable screening tool for the detection of stricture [163]. To overcome this, a statistical model based on uroflowmetry parameters was developed and was found to predict urethral stricture with a sensitivity of 80–81% and a specificity of 77–78% [163]. Uroflowmetry is usually combined with ultrasound (US) estimation of PVR to identify patients with urinary retention who may require emergent bladder drainage. Uroflowmetry parameters can also be used for monitoring patients and in the assessment of treatment response (see section 11. Follow-up).

Urodynamic studies are not indicated in the vast majority of patients with urethral stricture disease. In patients with suspected bladder dysfunction (e.g., severe storage LUTS, history of irradiation or neurological disease), an assessment of bladder function may help surgical decision making and patient counselling. Similarly, when there is concern that flow impairment or increased PVR are due to detrusor underactivity or an acontractile detrusor, a urodynamic study may help predict the likelihood that the patient would need to perform intermittent self-catheterisation (ISC) post-operatively. The only urodynamic parameter found to distinguish a diagnosis of urethral stricture from BPO is urethral closure pressure which is lower in the former due to the constrictive nature of the obstruction (22.07 vs. 28.4 cm H_2O, p=0.0039, r=0.61, BPO vs. stricture) [164].

Summary of evidence	LE
Uroflowmetry pattern interpretation by use of a statistical model was found to be predictive of urethral stricture disease.	3

Recommendation	Strength rating
Perform uroflowmetry and estimation of post-void residual in patients with suspected urethral stricture disease.	Strong

5.2.1.4 Urethrography

Retrograde urethrography (RUG) has widely been used as the investigation of choice for evaluating the stricture presence, location, length, and any associated anomalies (e.g., false passages, diverticula) [165].

The reported sensitivity and specificity of RUG in the diagnosis of strictures is 91% and 72%, respectively [166]. The positive predictive value (PPV) was 89% and the negative predictive value (NPV) was 76% [166]. Most reports suggest that RUG underestimates stricture length [167, 168]. Interpretation of RUG findings by urologists were found to be more accurate at predicting urethral stricture location and length as compared to evaluation by an independent physician [169].

Limitations of RUG include difficulty assessing very distal strictures and assessing the proximal extent of strictures which are too narrow to permit passage of adequate contrast. Combining a RUG with voiding cystourethrography (VCUG) can allow adequate visualisation of the urethra proximal to the stricture and a more accurate assessment of stricture length in (nearly) obliterative strictures, stenoses and gap in pelvic fracture urethral injury (PFUI) [170, 171]. In addition, urethrography provides only a two-dimensional assessment of stricture and the results may be affected by the amount of penile stretch [172], degree of pelvic rotation and patient body habitus [173]. Risks of the procedure include infection, discomfort [164], contrast reaction from intravasation of contrast [174] in addition to the risk of radiation exposure. Urethrographic clamp devices (Brodny, Knutson) are available and were found to be less painful than using the Foley catheter technique [175].

Summary of evidence	LE
Retrograde urethrography is a widely available and easy to perform method of diagnosing and assessing urethral stricture but may underestimate stricture length.	2a
Retrograde urethrography alone is not able to assess stricture length (or gap) in obliterative strictures or stenosis.	2a
Urethrographic clamp devices are less painful than using the Foley catheter technique.	2a

Recommendations	Strength rating
Perform retrograde urethrography to assess stricture location and length in men with urethral stricture disease being considered for reconstructive surgery.	Strong
Combine retrograde urethrography with voiding cystourethrography to assess (nearly)-obliterative strictures, stenoses and pelvic fracture urethral injuries.	Strong
Use clamp devices in preference to the Foley catheter technique for urethrographic evaluation to reduce pain.	Weak

5.2.1.5 Cystourethroscopy

Cystourethroscopy allows for accurate visual detection of a suspected stricture or can rule out a stricture as cause of obstructive voiding [166]. It can detect narrowing of the urethral lumen before changes in uroflowmetry and symptoms [145]. Cystourethroscopy can also assess the presence of LS or other pathology but cannot usually assess stricture length as the calibre of most cystoscopes is greater than most symptomatic strictures [176]. To overcome this, use of smaller calibre ureteroscopes (6.5 Fr and 4.5 Fr) has been reported [176]. This also allows an assessment of the bladder prior to surgery and may identify other pathology such as bladder stones. Cystourethroscopy is particularly helpful for diagnosing proximal BMS which may be missed on RUG [177] .

Retrograde urethroscopy combined with antegrade cystoscopy via the suprapubic tract may be used to evaluate PFUI and plan the surgical approach. It allows an assessment of the length of the defect, the competence of the bladder neck, the involvement of the bladder neck in scarring in addition to identifying the presence of bony spicules or other abnormalities (e.g., fistulae, stones) [178]. Combined retrograde and antegrade cystoscopy was found to provide similar estimates of length of urethral defect in patients with PFUI as combined retrograde and antegrade cystourethrography, but was more likely to detect fistulae, false passages, and calculi [178].

Summary of evidence	LE
Cystourethroscopy will reliably detect the presence of a urethral stricture.	3
Combined retrograde urethroscopy and antegrade cystoscopy is more accurate than retrograde and voiding cystourethrography at identifying associated abnormalities such as fistulae, false passages, and calculi in patients with PFUI.	3

Recommendations	Strength rating
Perform cystourethroscopy as an adjunct to imaging if further information is required.	Weak
Combine retrograde urethroscopy and antegrade cystoscopy to evaluate pelvic fracture urethral injuries as an adjunct to imaging if further information is required.	Weak

5.2.1.6 Ultrasound

Ultrasound of the urethra or sonourethrography (SUG) provides a non-invasive three-dimensional assessment of anterior urethral stricture disease; including stricture location, length, and the degree of associated spongiofibrosis [179].

Several studies have compared SUG to RUG and cystoscopic or intraoperative findings. Sonourethrograpy was found to be more accurate at diagnosing stricture presence compared to RUG [175, 180]. Sonourethrography was also found to more accurately estimate stricture length (94% correlation with intraoperative findings) than RUG (59% correlation with intraoperative findings) ($p < 0.001$) [168]. A further study showed similar findings and found that the closest correlation for stricture length at operation was for strictures in the penile urethra [167]. Intraoperative sonourethrogram findings have also been found to change the planned reconstructive approach (based on pre-operative retrograde urethrogram) in 19% of men undergoing anterior

urethral reconstruction [173]. Sonourethrography incorporating real-time elastography can provide a qualitative and quantitative assessment of spongiofibrosis [181, 182]. The clinical relevance of assessing the degree of spongiofibrosis pre-operatively remains to be established. Three-dimensional reconstruction of sonographic images is investigational at present [183].

The advantages of SUG are that it can be performed in the outpatient setting, provides information on the degree of spongiofibrosis and its relatively low cost [179]. Limitations of the technique include lower sensitivity for detection of strictures in the bulbar urethra, operator dependency, and the need for urethral distension requiring intraurethral anaesthesia. Sonourethrography requires specialised training in the use of US and is currently not in widespread usage.

Table 5.1: Diagnostic accuracy of sonourethrography compared to other modalities and surgical findings

Study	N	Segment of urethra studied	Comparator	Accuracy of SUG		
				Diagnosis	Location	Length
Berne-Mestre *et al*. 2018 [175]	113	Anterior and posterior	RUG, VCUG, surgical findings	SUG more accurate than RUG ($p < 0.05$)	-	-
Ravikumar *et al*. 2014 [180]	40	Anterior and posterior	RUG, VCUG, surgical findings	Anterior: SUG 100% sensitivity, 100% specificity Posterior: SUG 75% sensitivity, 50% specificity.	-	-
Kalabhavi *et al*. 2018 [168]	30	Anterior	RUG, surgical findings	-	-	-
Krukowski *et al*. 2018 [167]	66	Anterior	RUG, surgical findings	-	-	-

N = number of patients; RUG = retrograde urethrography; SUG = sonourethrography; VCUG = voiding cystourethrogram.

5.2.1.7 Magnetic resonance imaging

Magnetic resonance imaging (MRI) has been used to image PFUIs, posterior urethral stenoses and anterior urethral strictures.

Several studies have compared MRI urethrogram to RUG and intraoperative findings. Magnetic resonance imaging urethrogram was found to be as accurate as RUG at detecting stricture site in anterior urethral strictures [184]. In terms of stricture length both MRI urethrogram and RUG reliably correlated with intraoperative findings [184]. On the other hand, a further study of patients with anterior urethral strictures found MRI urethrogram stricture length to correlate more closely with surgical findings than RUG [185].

In a mixed group of anterior urethral strictures and posterior urethral stenoses, MRI urethrogram was as accurate (sensitivity = 100%, specificity = 91.7%) as combined RUG and sonourethrography (sensitivity = 100%, specificity = 91.7%) at diagnosing strictures [186]. There was no significant difference in the measurement of stricture length [186]. In a further study of patients with posterior urethral stenosis, MRI estimation of stenosis length correlated more closely with operative findings compared to RUG [187]. In patients with PFUI, MRI measurement of pubo-urethral stump angle (angle between long axis of pubis and line between the distal end of the proximal urethral stump and lower border of inferior pubic ramus) was predictive of an elaborated approach on multivariate analysis [188].

Magnetic resonance imaging was also found to be more accurate at diagnosing associated pathologies e.g., diverticula, tumours, fistulae, and stones [186]. In cases of fistulation between the urinary tract and pubic symphysis after irradiation for prostate cancer, the fistula tract can be clearly demonstrated on MRI [189]. Other imaging modalities, including computed tomography (CT), may fail to identify the tract and the problem may be misdiagnosed as isolated osteomyelitis of the pubic bone leading to medical management with antibiotics rather than surgical excision [189].

The main advantage of MRI is greater anatomical detail, which is countered by the expense of the procedure and the greater complexity in interpreting images. The technique is not commonly used for routine situations, but it may be helpful in diagnosing associated pathologies which may alter patient management.

Table 5.2: Diagnostic accuracy of MRI compared to other modalities and surgical findings

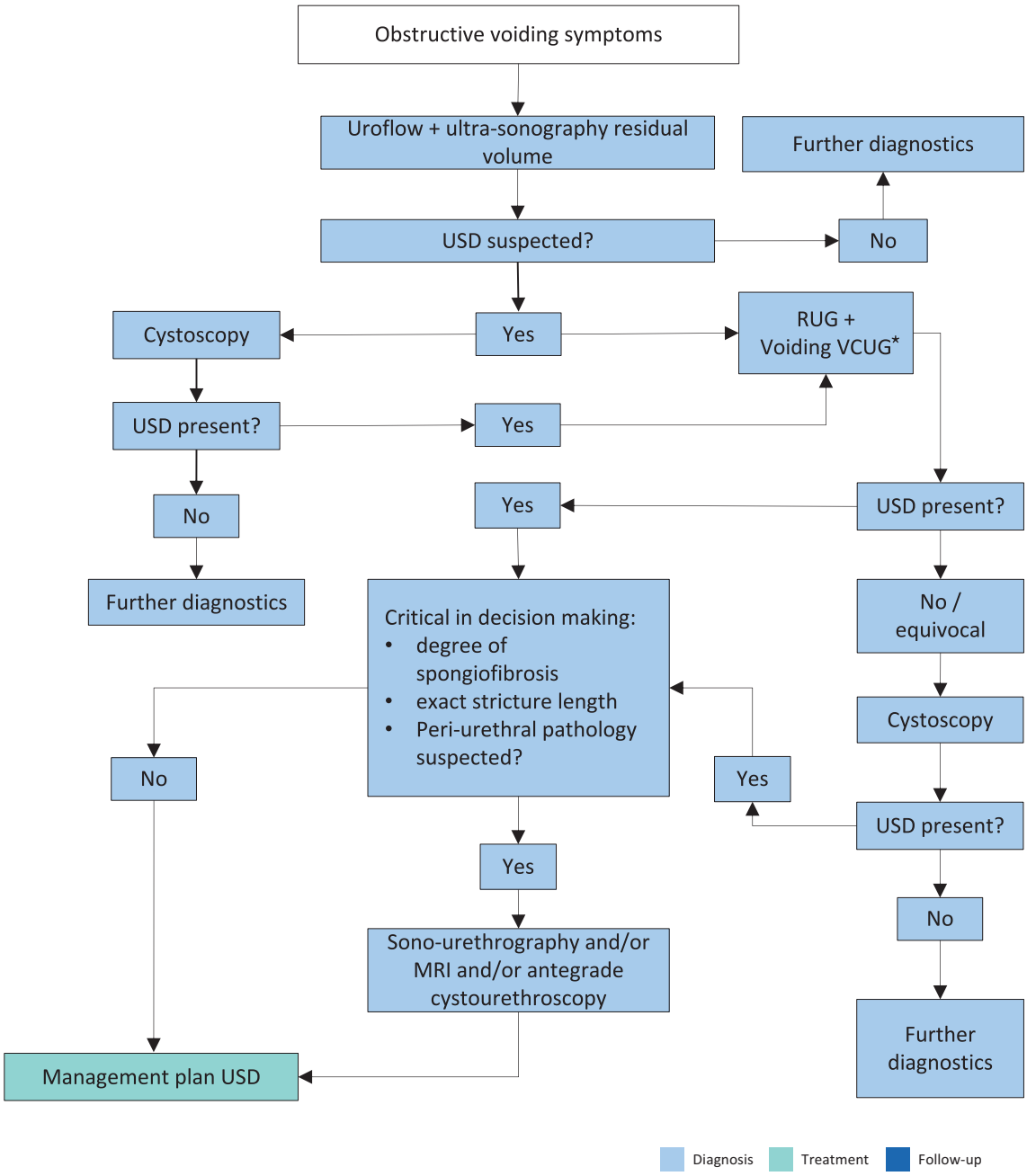
Study	N	Segment of urethra studied	Comparator	Accuracy of SUG		
				Diagnosis	Location	Length
Murugesan *et al*. 2018 [184]	32	Anterior	RUG, Surgical findings	MRI and RUG equivalent (100% sensitivity, 100% specificity)	-	-
Fath El-Bab *et al*. 2015 [185]	20	Anterior	RUG, Surgical findings	-	-	MRI more accurate than RUG.
El-Ghar *et al*. 2010 [186]	30	Anterior and posterior	RUG + SUG, Surgical findings	MRI and RUG equivalent (100% sensitivity, 91.7% specificity)	-	MRI and RUG equivalent.
Oh *et al*. 2010 [187]	25	Posterior	RUG + SUG, Surgical findings	-	-	MRI more accurate than RUG + VCUG.

MRI = magnetic resonance imaging; n = number of patients; RUG = retrograde urethrography; SUG = sonourethrography; VCUG = voiding cystourethrogram.

Summary of evidence	LE
Magnetic resonance imaging is more accurate than retrograde urethrography and voiding cystourethrography at determining length of posterior urethral stenoses and can detect alternative associated pathologies e.g., diverticula, fistulae.	2a

Recommendation	Strength rating
Consider magnetic resonance imaging urethrography as an ancillary test in posterior urethral stenosis.	Strong

Figure 5.1: Diagnostic flowchart of patients with suspected urethral stricture disease



**Use VCUG in case of (nearly-) obliterative strictures or stenosis.*
MRI = Magnetic resonance imaging; RUG = retrograde urethrography, USD = urethral stricture disease; VCUG = voiding cystourethrogram.

6. DISEASE MANAGEMENT IN MALES

6.1 Conservative options

6.1.1 ***Observation***

A stricture will usually result in diminution in flow once the calibre of the urethral lumen is < 10 Fr [144]. In other strictures (> 10 Fr), the diagnosis is often made by coincidence in asymptomatic patients because of a urologic examination for other reasons (e.g., cystoscopy, need for urethral catheterisation) [144]. Purohit *et al*., performed observation and repeated cystoscopic evaluation of 42 subclinical, incidentally encountered strictures (> 16 Fr). After a median follow-up of 23 months, only five (12%) strictures progressed to a low-grade stricture (11-15

Fr). No patient developed symptoms and none of them needed surgical intervention [144]. These patients are candidates for observation although no evidence exist on the long-term evolution of these strictures.

In a series of anatomic stricture recurrence (< 16 Fr) after urethroplasty, only 65% of patients were symptomatic [145]. Some asymptomatic patients refused further intervention because they had experienced substantial improvement after their primary urethroplasty. These patients were considered as functional "success" [145]. A multicentric study of the Trauma and Urologic Reconstructive Network of Surgeons observed an important discrepancy between cystoscopic recurrence and need for further intervention [143]. Patients with a large calibre (> 16 Fr) recurrence had a one and two-year need for intervention rate of 4% and 12%, respectively. Of note, patients with small-calibre (< 16 Fr) recurrence had a one and two-year need for intervention rate of only 41% and 49%. Patients who needed intervention had poorer PROMs suggesting clinical symptoms and bother. There is no information on long-term complications in patients with recurrences who did not undergo intervention. In cases of an asymptomatic stricture recurrence, it might be an option not to intervene but to perform regular follow-up.

Care must be taken about the term "asymptomatic" stricture (recurrence) as patients might conceal their bother and symptoms by different means (not drinking, social avoidance) and might only search for medical help once concealment is no longer tenable [190].

*6.1.2 **Suprapubic catheter***

Radiation-induced urethral strictures are a difficult to treat population as stricture-free rates for urethral reconstruction are lower compared to those in non-irradiated patients [191]. Fuchs *et al*., evaluated 75 patients who were initially treated by suprapubic diversion for radiation-induced isolated BMS [192]. Only 51% eventually decided to undergo urethroplasty after a mean follow-up period of 25 months. Although there was no significant difference in overall performance status between patients with a chronic suprapubic catheter vs. those undergoing urethroplasty, all patients with a poor performance score remained with a suprapubic catheter. Patients with concomitant stress urinary incontinence (SUI) opted more often to keep their suprapubic catheter as the SUI improved in 61% of cases. On the other hand, patients who kept their suprapubic catheter suffered from catheter-related complications in 27% of cases. Urinary diversion by ileal conduit was performed in 30% of patients who remained with a suprapubic catheter while this was only the case in 8% who underwent urethroplasty. A suprapubic catheter is also an option in frail patients not able to undergo surgery or in patients who do not want (further) urethral surgery and are willing to accept the complications of a suprapubic catheter [193].

Summary of evidence	**LE**
Patients with asymptomatic incidental (> 16 Fr) strictures have a low risk of progression and to develop symptoms.	3
Only half of the patients initially treated with a suprapubic catheter for radiation-induced bulbomembranous strictures will proceed with urethroplasty.	3

Recommendations	**Strength rating**
Do not intervene in patients with asymptomatic incidental (> 16 Fr) strictures.	Weak
Consider long-term suprapubic catheter in patients with radiation-induced bulbomembranous strictures and/or poor performance status.	Weak

6.2 Endoluminal treatment of anterior urethral strictures in males

The ability to treat the majority of strictures by less invasive and time-consuming means, offers obvious benefits particularly when specialist surgical services are not available, or patients simply prefer a more pragmatic immediately available solution.

*6.2.1 **Direct vision internal urethrotomy***

In contemporary practice, direct vision internal urethrotomy (DVIU) is commonly performed as a first-line treatment of urethral strictures [194]. It is usually performed under general or spinal anaesthesia in well-resourced countries but shown to be well tolerated under local anaesthesia with or without sedation [195].

6.2.1.1 Indications of "cold knife" direct vision internal urethrotomy

6.2.1.1.1 Direct vision internal urethrotomy for primary stricture treatment

In the only high-level evidence study, Steenkamp *et al*., randomised 210 patients with seemingly comparable non-obliterative strictures at all locations of the urethra to either filiform dilatation vs. DVIU with local anaesthesia on an outpatient basis [196]. They collected objective data with RUG performed at seven follow-up visits (3, 6, 9, 12, 24, 36 and 48 months). This unique study showed that urethral dilatation is equally effective as DVIU but both procedure modalities become less effective with increasing stricture length (see section 6.2.1.1.3.1).

A retrospective cohort series on the primary treatment of patients with iatrogenic urethral strictures reported a significantly poorer patency rate for DVIU compared to urethroplasty techniques (32.2 versus 82.4-83.5%) [197].

Patency rates vary considerably between 8% and 77% after DVIU (predominantly without prior urethroplasty) in retrospective cohort studies with minimum follow-up of one year [67, 198-204] (Table 6.1). Median time to recurrence was less than twelve months in most series [67, 198-202]. This large variation in patency rate can be in part explained by the heterogeneous nature of the strictures and various definitions of patency used by the authors in these series. Indication to perform DVIU is dependent on various stricture characteristics that are prognostic for a successful outcome.

Table 6.1: Results of DVIU in series with minimum follow-up > 12 months

Study	N	Age (years)	Follow-up (months)	Location	Length (cm)	Previous interventions	TTR (months)	Patency rate (%)
Al Taweel *et al*. [200]	301	37 (range: 17-82)	36	Bulbar: 227 (75%)	1.3 (0.4-4.2)	Primary: 47%	10	8.3
				Penile: 50 (17%)		Recurrent: 53%	-	-
				Penobulbar: 24 (8%)				
Barbagli *et al*. [199]	136	37 (IQR: 25-48)	55 (range: 36-92)	Bulbar: 100%	1-2 cm: 45%	Primary: 100%	25	57
					2-3 cm: 40%			
					3-4 cm: 15%			
Kluth *et al*. [198]	128	64 (SD: 16)	16 (IQR:6-43)	Penile: 15 (12)	NR	Primary: 66%	8	52
				Bulbar: 112 (88)		Recurrent: 34%	-	-
				Unknown: 1 (1%)				
Pal *et al*. [201]	186	39 (SD:15)	1st DVIU: 58 (SD: 15)	bulbar: 100%	NR	Primary: 69%	8.5	1st DVIU: 30
			2nd DVIU: 56 (SD: 15)			Repeat: 31%	-	2nd DVIU: 23
			3rd DVIU: 45 (SD: 15)					3rd DVIU: 13
Launonen *et al*. [202]	34	6 (range: 0-16)	79 (range: 7-209)	Bulbar: 74%	≤ 2 cm: 85%	Primary: 100%	4	26%
				Penile: 21%	> 2 cm: 15%			
				Penobubar: 6%	-			
Redon-Galvez *et al*. [203]	67	57 (range: 15-91)	40 (range: 12-120)	Penile:9%	≤ 1 cm: 82%	Primary: 90%	< 24	63%
				Bulbar: 64%	> 1 cm: 18%	Repeat: 10%	-	-
				VUA: 21%				
				Membranous: 6%				
Güler Y. [197]	234	57 (range: 22-74)	47 (range: 24-56)	Penile: 34%	2.5 (0.4-5)	Primary: 100%	-	34%
				Bulbar: 59%				30%
				Membranous: 6%				33%
Harraz *et al*. [204]	430	50 (SD: 15)	29 (range: 3-132)	Bulbar: 100%	< 2 cm	NR, prior urethroplasty excluded	NR	58%

Yürük *et al*. [67]	193	65 (SD: 13)	36 (SD: 12)	Bulbar: 100%	< 1 cm: 140 (73%)	0%	87% of recurrence ≤ 3	77%
					1-2 cm: 21 (11%)	-	100% of recurrence ≤ 6	-
					2-3 cm: 32 (17%)			

DVIU = Direct vision internal urethrotomy; IQR = interquartile range; N = number of patients; NR = not reported SD = standard deviation; TTR = time to recurrence.

6.2.1.1.2 Direct vision internal urethrotomy for recurrent strictures and as salvage treatment after failed urethroplasty

In the OPEN trial, a recurrent stricture was defined as at least one previous failed intervention (endoscopic urethrotomy, urethral dilatation, urethroplasty) [205]. The previous intervention was predominantly DVIU. Despite poor recruitment, 108 and 112 patients were randomised to urethroplasty and DVIU respectively in a 24-month study protocol. Both groups had a similar improvement in voiding score symptoms after intervention. However, patients undergoing urethroplasty had 2.6 higher odds of experiencing an improvement of > 10 ml/s in their maximum urinary flow compared to those undergoing urethrotomy (p=0.001) [205]. Need for re-intervention was observed in 13.8% vs. 25.9% of cases respectively allocated to urethroplasty and DVIU resulting in a 48% lower risk for re-intervention with urethroplasty (HR: 0.52; 95% CI: 0.31-0.89; p=0.017) [205]. Of note, self-dilatation was not considered a re-intervention [205]. Despite more re-interventions in the DVIU group, both treatments resulted in a similar improvement in quality of life but with a higher cost for urethroplasty with the limitation that the follow-up is only two years. [206]. Direct vision internal urethrotomy is also used as salvage treatment for recurrent strictures after urethroplasty. Brown *et al.*, used DVIU for stricture recurrence (mean length: 4 cm; range: 1.5-7 cm) after excision and primary anastomosis (EPA), buccal mucosa grafts (BMG) urethroplasty and penile skin graft urethroplasty [207]. Patency was obtained in thirteen out of 37 cases (35%) after a single DVIU. After free graft urethroplasty (FGU), a short, veil-like stricture (or "diaphragm") might develop at the distal or proximal end of the graft. Rosenbaum *et al.*, used DVIU to a selected cohort of 43 patients with a short (< 1 cm), veil-like stricture after BMG urethroplasty [208]. After a mean follow-up of twelve months, patency rate was 51%.

6.2.1.1.3 Predictors of failure of "cold knife" direct vision internal urethrotomy

Several groups tried to identify prognostic factors to predict which patients are most likely to fail initial treatment (Table 6.2).

In the absence of well-designed, adequately powered multi-centre trials it is difficult to answer the question as to which clinical factors are predictive of failure of DVIU in men with urethral strictures. However, based on the predictors evaluated above, one can summarise that the best candidates are previously untreated patients with a single, short (max. 2 cm) bulbar stricture. Barbagli *et al.*, reported a five-year patency rate of 71% for patients with untreated short (1-2 cm) bulbar urethral strictures [199].

Table 6.2: Predictors for urethral patency after direct vision internal urethrotomy

Author	Location	Length	Calibre	Multiplicity	Prior DVIU
Steenkamp *et al*. [196] / Heyns [209]	RR for recurrence penile vs. bulbar: 1.85 (95% CI: 0.94 to 3.67, p = 0.077)	< 2 cm: 60% (@12 months)	NR	NR	None: 50-60% (@48 months)
	-	2-4 cm: 50% (@12m)	-	-	1: 0-40% (@48 months)
	-	> 4 cm: 20% (@12 months)	-	-	2: 0% (@24 months)
Al Taweel *et al*. [200]	Bulbar: 11%	< 1 cm: 27%	NR	NR	0: 12.1%
	Penile: 0%	1-2 cm: 0%	-	-	1: 7.9%
	Penobulbar: 0%	> 2 cm: 0%	-	-	> 1: 0%

Barbagli *et al*. [199]	NA	1-2 cm: 71% (@60 months)	pQ_{max} < 5 ml/s: 31%	NA	0: 62%
	-	2-3 cm: 51% (@60 months)	pQ_{max} 5-8 ml/s: 53%	-	1: 37%
	-	3-4 cm: 39% (@60 months)	pQ_{max} > 8 ml/s: 83%	-	-
Kluth *et al*. [198]	Location no predictor	NR	pQ_{max} no predictor	NR	0: 60%
	-	-	-	-	≥ 1: 39%
Pal *et al*. [201]	NA	< 1 cm: 45%	NR	Single: 35%	0: 30%
	-	1-1.5 cm: 0%	-	Multiple: 0%	1: 23%
	-	> 1.5 cm: 0%	-	-	2: 13%
Launonen [202]	Bulbar: 76%*	< 2 cm: 83%*	NR	NR	0: 26%
	Penile: 71%*	> 2 cm: 0%*	-	-	1: 33%
	-	-	-	-	2: 26%
	-	-	-	-	3: 11%
	-	-	-	-	4: 0%
Redon-Galvez [203]	NR	≤ 1 cm: 71%	NR	NR	NR
	-	> 1 cm: 25%	-	-	-
Güler Y [197]	Bulbar: 30%	<1.85 cm: OR 0.86 (95% CI: 0.74-0.99; p=0.042)	NR	NR	NR
	Penile: 34%				
	Membranous: 33%				

DVIU = Direct vision internal urethrotomy; NA = not applicable; NR = not reported; pQ_{max} = pre-operative maximum urinary flow; RR: relative risk; OR: Odds ratio; CI: confidentialtiy interval.
**patency rates are reported after repetitive treatments.*

6.2.1.2 Indications of "hot-knife" direct vision internal urethrotomy

6.2.1.2.1 Laser urethrotomy

Lasers available for urological applications, including Neodymium:YAG, Argon, Holmium:YAG, Potassium titanyl phosphate (KTP) and Tm:Yag, have been used for the treatment of urethral strictures. A SR identified four RCTs comparing laser urethrotomy and the "cold knife" urethrotomy. All studies were limited by short-term outcome evaluation and none of these four studies specified the results based on the location of the stricture. Two of these studies reported specific recurrence rates and meta-analysis showed a relative risk (RR) for recurrence of 0.55 (95% CI: 0.18-1.66; p=0.29), 0.39 (95% CI: 0.19-0.81; p=0.01) and 0.44 (95% CI: 0.26-0.75; p=0.003) in favour of laser urethrotomy after three, six and twelve months respectively [210]. Jin *et al.*, performed a SR including 44 case series on laser urethrotomy or "cold knife" DVIU [211]. This included nineteen articles on laser urethrotomy and 25 articles on "cold knife" DVIU. The overall weighted average stricture-free rate was 74.9% (371/495) and 68.5% (1874/2735) for laser vs. "cold knife" DVIU, respectively (p=0.004). Although statistically significant, the results must be interpreted with caution because of heterogeneity and because no details are provided on follow-up duration. Specifically looking at first DVIU, laser and "cold knife" DVIU obtained a stricture-free rate of 58.6% and 42.7%, respectively and the difference was no longer statistically significant (p=0.09). At the bulbar urethra, laser and "cold knife" DVIU yielded a stricture-free rate of 52.9% and 60%, respectively (p=0.66) [211].

After publication of this SR, the EAU Guideline Panel scope search identified three additional RCTs [212-214]. In the RCT of Yenice *et al.*, patients with a primary, bulbar stricture were randomised either to "cold knife" DVIU (n=29) or holmium:YAG laser urethrotomy (n=34). After twelve months follow-up, no significant difference in patency rate was identified (79% for "cold knife" DVIU vs. 68% for laser urethrotomy, p=0.3) [213]. In their RCT, Chen *et al.*, reported a better patency rate after one year with laser (n=24) compared to "cold knife" (n=22) DVIU (respectively 88% vs. 18%; p < 0.05). However, after two years the benefit for laser disappeared and after five years both techniques showed a low patency rate: 9% for "cold knife" DVIU vs. 12% for laser DVIU (p > 0.05) [212]. Gamal *et al.*, randomized patients between "cold knife" DVIU (n=40) and Holmium:Yag laser DVIU (n=40). At one year, they found an equally effective improvement of maximum urinary flow in both groups.

6.2.1.2.2 Plasmakinetic (bipolar) urethrotomy

Cecen *et al.*, conducted an RCT comparing plasmakinetic with "cold knife" DVIU (n=136) [215]. They reported patency rates for plasmakinetic and "cold knife" urethrotomy at nine months in respectively 86% and 70% of cases (p=0.025). At eighteen months, patency rates for plasmakinetic and "cold knife" urethrotomy were 63% and 67%, respectively (p=0.643) [215]. A prospective cohort study on primary strictures < 2 cm reported a patency rate at twelve months in 23/30 (77%) cases for plasmakinetic DVIU vs. 19/30 (63%) cases with "cold knife" DVIU (p=0.04) [216]. A retrospective case series (n=27) reported a 74% patency rate for short (1-2.5 cm) strictures after a mean follow-up of fourteen months [217]. They reported negligible blood loss during the procedure and no post-operative incontinence.

Based on the conflicting results described above and considering the heterogeneity of series and absence of long-term follow-up, overall, the available studies do not support the efficacy of one technique of DVIU over another. Given the similar complication rates between techniques (see section 6.2.1.3), no recommendation can be made in favour of one technique over another.

6.2.1.3 Complications of direct vision internal urethrotomy

6.2.1.3.1 Complications of "cold knife" direct vision internal urethrotomy

An overall complication rate of 6.5% was reported in a SR of Jin *et al.*, based on twelve articles including 1,940 patients [211] (Table 6.3).

Notably, erectile dysfunction (ED) was reported in 5.3% of cases in this review [211]. In addition, Graversen *et al.*, reported ED in eleven out of 104 (10.6%) patients [218]. This risk appears higher in strictures located in the penile urethra and, in addition to the poor patency rates, the use of DVIU in the penile urethra must be discouraged [218, 219].

6.2.1.3.2 Complications of "hot knife" direct vision internal urethrotomy

The SR of Jin *et al.*, reported a total complication rate of 11.8% (39/330) [211] (Table 6.3).

6.2.1.3.3 Complications of "cold knife" vs. "hot knife" direct vision internal urethrotomy

In a SR of RCTs comparing "cold knife" DVIU vs. laser DVIU, only 1/4 series reported complications [210].
In the laser group, an 8.9% complication rate was found due to contrast extravasation to the perineum and stricture recurrence. For the "cold knife" DVIU, a 15.5% complication rate was reported related to bleeding [210]. Two later RCT's reported similar rates of urinary extravasation [212, 213] and urinary incontinence (UI) [212] with both techniques.

The SR of retrospective case series of Jin *et al*., found no significant differences in the incidence rates of UI, urinary extravasation and UTI between laser and "cold knife" DVIU [211]. However, urinary retention and haematuria were more frequent with laser compared to "cold knife" DVIU [211]. Conversely, In the series of Yenice *et al*., haematuria was only reported after "cold knife" DVIU but not after laser DVIU (p=0.6) [213] (Table 6.3).

Table 6.3: Complications after "cold knife" DVIU vs. laser DVIU

Study/Complication	"Cold knife" DVIU (%)	Laser DVIU (%)	p-value
Jin *et al*. [211]			
Urinary extravasation	2.9	3.1	0.938
Urinary incontinence	4.1	2.1	0.259
Urinary tract infection	2.1	2.7	0.653
Urinary retention	0.4	9	< 0.0001
Haematuria	2	5.2	0.034
Epididymitis	0.5	NR	NA
Fever	2.3	NR	NA
Scrotal abscess	0.3	NR	NA
Erectile dysfunction	5.3	NR	NA
Urinary tract irritation	NR	11.4	NA
Urinary fistula	NR	1.5	NA

Dysuria	NR	5.1	NA
Yenice *et al*. [213]			
Urinary extravasation	0	2.9	0.6
Haematuria	10	0	
Chen *et al*. [212]			
Urinary extravasation	9.1	4.2	0.5
Urinary incontinence	4.5	4.2	

DVIU = direct vision internal urethrotomy; NA = not applicable; NR = not reported.

6.2.1.3.4 Complications of direct vision internal urethrotomy vs. dilatation

A Cochrane review found no significant differences for overall intra-operative complications (single dilatation vs. DVIU respectively 14% vs. 11%; RR: 0.75; 95 CI: 0.36-1.55) nor for individual complications (difficulty urinating, haematuria, false passage, pain, knotting/breaking/bending filiform leader) [196, 220]. The low rate of false passage for both DVIU and dilatation (respectively 0.96 and 0.94%) might be explained by the systematic use of a filiform leader in both groups which was inserted endoscopically in the dilatation group followed by coaxial dilatators [196, 220].

A small retrospective study comparing balloon dilatation (n=31) with DVIU (n=25) showed less urethral bleeding (6.5 vs. 32%; p=0.017) and UTI (3.2 vs. 24%; p=0.037) with balloon dilatation [221].

Apart from acute peri-operative complications described above, the stricture length and number of strictures were reported to increase after DVIU. Other authors mention that repeat urethral manipulations (DVIU and/or dilatation) can increase stricture complexity and delays time to urethroplasty [222].

6.2.1.3.5 Complications of "cold knife" direct vision internal urethrotomy vs. urethroplasty

The OPEN-trial reported adverse events of any type in 61% and 26.1% after urethroplasty (all types) and DVIU respectively [205]. In the urethroplasty group, mouth pain (related to oral mucosa graft [OMG] harvesting) and wound infection was noted as complication in respectively 14.6% and 4.9% of cases. Erectile dysfunction was 4.9% and 2.6% after urethroplasty and DVIU, respectively. Serious adverse events were reported in 8.5% and 8.7% after urethroplasty and DVIU respectively [205].

Summary of evidence	**LE**
Direct vision internal urethrotomy performs poorly in penile strictures. Direct vision internal urethrotomy at the penile urethra might provoke venous leakage from the corpora cavernosa with subsequent risk of erectile dysfunction.	1b
Increased stricture length is associated with higher risk of failure of direct vision internal urethrotomy (DVIU).	1b
In selected patients with a primary, single, short (< 2 cm) and non-obliterative bulbar stricture, a five-year stricture-free rate of up to 77% can be expected.	3
Direct vision internal urethrotomy has a stricture-free rate of 51% if performed for a short, veil-like recurrent stricture after prior bulbar urethroplasty.	3
There is conflicting evidence that "hot knife" (laser, plasmakinetic) DVIU would be superior compared to "cold knife" DVIU after more than one year of follow-up.	1a

Recommendations	**Strength rating**
Do not use direct vision internal urethrotomy (DVIU) for penile strictures.	Strong
Do not use DVIU/dilatation as solitary treatment for long (> 2 cm) segment strictures.	Strong
Perform DVIU/dilatation for a primary, single, short (< 2 cm) and non-obliterative stricture at the bulbar urethra.	Weak
Perform DVIU/dilatation for a short, veil-like recurrent stricture after prior bulbar urethroplasty.	Weak
Use either "hot" or "cold knife" techniques to perform DVIU depending on operator experience and resources.	Weak

6.2.2 *Single dilatation*

6.2.2.1 *Modalities of dilatation and results*

Dilatation can be done in the office, under local anaesthesia and without complex resources [223, 224]. With dilatation, the urethral mucosa at the stricture site is stretched and the scarring is disrupted. This is opposed to DVIU where the stricture is incised. However, both treatment modalities use the same principle to achieve urethral patency: a breach of the urethral mucosa at the site of the stricture in which re-epithelialisation should occur faster than wound contraction [220].

When dilators are used to dilate bulbar urethral strictures, considerable experience is required to avoid accidental perforation of the urethra at the level of the stricture. In order to reduce the risks (esp. false passage, spongiosal perforation, urethral bleeding) of "classic" blind dilatation with rigid sounds [224], other strategies have been developed and evaluated in which the dilatation is visually controlled after a guidewire has been inserted (Table 6.4).

Although no direct comparative studies of blind vs. visually controlled dilatation are available, several studies have reported a low complication rate with visually controlled modifications of dilatation. The recurrence rate largely varies between 23.5-64.5% (Table 6.4).

Table 6.4: Results of visually controlled dilatation

Study	Technique	N	FU (mo)	recurrence	Definition of failure	Complications			
						Haematuria	False passage	Procedural failure	UTI
Hosseini *et al*. [224]	Nelaton urethral catheters	333	43 (36-52)	138 (41,4%)	Need for additional intervention	12 (3.6%)	2 (0.6%)	NR	15 (4.5%)
Kallidonis *et al*. [225]	Coaxial S-curved	310	12	90 (33%)	No recurrence @1 yr with maximum one additional procedure	11 (3.5%)	0 (0%)	7 (2.2%)	33 (10.6%)
Nomikos *et al*. [226]	Amplatz + DVIU + ISD (1 yr.)	34	12	8 (23.5%)	Stricture recurrence on urethroscopy/ urethrography	2 (5.8%)	NR	NR	3 (8.8%)
Yu *et al*. [221]	Balloon	31	15 (5-36)	20 (64.5%)	Need for subsequent urethroplasty	2 (6.5%)	0 (0%)	NR	1 (3.2%)

DVIU = direct vision internal urethrotomy; FU = follow-up; ISD = intermittent self-dilatation; mo = months; N = number of patients; NA = not applicable; NR = not reported; UTI = urinary tract infection; yr = year.

6.2.2.2 *Effectiveness of dilatation compared with direct vision internal urethrotomy*

A SR identified only one prospective RCT comparing dilatation with DVIU and failed to detect any differences [196, 220]. In a small (n=56) retrospective cohort study, the three-year estimated stricture recurrence-free survival was 35.5% and 28% for respectively balloon dilatation and DVIU (p=0.21) [221].

At present, there is lack of evidence to support the claim that dilatation is superior to DVIU (or *vice versa*) and therefore, the indications for single dilatation are the same as for DVIU.

Repetitive dilatation/DVIU with curative intent (see also section 6.2.1.1.3.6 Previous interventions) should be avoided as no long-term freedom of recurrence can be expected [223] and because of the significant risk of increasing stricture length and complexity and prolonging the time to urethroplasty (which has better patency rates) [222].

Summary of evidence	LE
Visually controlled dilatation after endoscopic or fluoroscopic guidewire placement has a low complication rate.	3

Repetitive dilatations/direct vision internal urethrotomy have no long-term freedom of recurrence and increase stricture complexity.	1b

Recommendations	Strength rating
Use visually controlled dilatation in preference to blind dilatation.	Weak
Do not perform repetitive (> 2) direct vision internal urethrotomy/dilatations if urethroplasty is a viable option.	Strong

*6.2.3 **Post-dilatation/direct vision internal urethrotomy strategies***

Several strategies have been developed and evaluated to prevent wound contraction, improve the stricture-free rate and time to stricture recurrence after dilatation or DVIU.

It is noteworthy that these strategies tend to stabilise the stricture rather than to keep the patient stricture-free and the reported outcomes should be understood in this respect.

6.2.3.1 Intermittent self-dilatation

6.2.3.1.1 Results

A SR identified six randomised and quasi-randomised trials comparing intermittent self-dilatation (ISD) with no ISD with a follow-up between eight and 24 months [227]. Stricture recurrence was reduced in men performing ISD (85/197, 43%) vs. those who did not (128/207, 62%) (RR: 0.70; 95% CI: 0.48-1.00; p=0.05). There was significant heterogeneity, and the quality of included studies were very low, which led the authors to conclude there is uncertainty about the estimate [227]. This review found no significant difference in adverse events between ISD and no ISD (RR: 0.60; 95% CI: 0.11-3.26; p=0.56) [227]. One trial containing 48 patients found no significant difference in six vs. twelve months duration of ISD (RR: 0.67; 95% CI: 0.12-3.64) and another trial (n=59) found no significant difference from using a low-friction hydrophylic vs. a polyvinyl chloride catheter (RR: 0.32; 95% CI: 0.07-1.40) [227]. Other studies have been published after this SR of 2014. Chhabra *et al*., reported that patients complying with ISD after dilatation had a lower need for re-intervention than those who did not, 12.3% vs. 20.5% respectively (p=0.2) [228]. After a mean follow-up of 25 months, Greenwell *et al*., found a need for subsequent intervention in 13/31 (42%) men performing ISD vs. 47/95 (49%) who did not (p=0.46). The number of reoperations in patients with need for subsequent intervention was lower in the group performing ISD vs. those who did not (2.6 vs. 3.4). No major complications were reported in both groups [229].

6.2.3.1.2 Complications

The potential benefit of ISD in stabilising the stricture must be balanced against the drawbacks. Commonly reported complications are urethral bleeding (7.1%) [230] and UTI/epididymitis (4.7-18.1%) [231, 232]. A multicentric prospective study (n=85) reported that respectively 35% and 26% of patients had moderate to severe difficulties in catheterisation and respectively 32% and 17% of patients suffered moderate to severe pain while performing ISD. This had a serious impact on QoL which was rated moderate and poor in 32% and 55% of patients, respectively [33]. Younger age was identified as predictor for poor QoL, and QoL was more impaired in proximal stricture location (posterior and bulbar) [33]. In a study of 286 patients (mainly > 60 years old) performing ISD, 20% experienced problems with ISD and 33% had at least one infection annually. After a mean follow-up of 58 months 67% still continued with ISD [233]. Khan *et al*., reported eight “drop-outs” of 30 (26.7%) men randomised to ISD [232]. Of these eight “drop-outs”, two were unable to perform ISD and one stopped because of pain.

As mentioned above, repetitive dilatation (including ISD) increases stricture complexity and delays time to urethroplasty [222, 234].

6.2.3.1.3 Intermittent self-dilatation combined with intra-urethral corticosteroids

To delay wound contraction at the stricture site, intra-urethral corticosteroids (as a catheter lubricant) have been used to improve the results of ISD. In 2014, a SR identified three prospective RCTs comparing ISD and local steroid (triamcinolone) ointment vs. ISD without local steroid ointment [235]. These three studies included a total 67 and 68 patients randomised to local steroid, or not, with a follow-up ranging between twelve and 36 months. There were fifteen (22.4%) recurrences in the steroid group and 25 (36.7%) in the control group (OR: 0.51; 95% CI: 0.24-1.10; p=0.09) [235]. Time to recurrence was longer in the steroid group vs. the control group (weighted mean difference = 0.29; 95% CI: 0.08-1.00; p=0.05). There was no difference in adverse events between groups [235].

Since 2014, two additional RCTs have been published. Ergun *et al*., evaluated patients after DVIU for primary short (< 2 cm), bulbar (82%) or posterior (18%) strictures that were further randomised between ISD (n=30) and ISD + triamcinolone ointment (n=30) for six weeks. Stricture recurrence rate after 24 months was not significantly different between ISD and ISD + triamcinolone (respectively 33.3 and 30%) [236]. On the other hand, Regmi *et al*., found a lower stricture recurrence rate (22% vs. 46%, p=0.04) in patients performing ISD + triamcinolone (n=27) vs. ISD alone (n=28) [237]. In this study, median time to recurrence was 7.4 ± 4.5 months vs. 11.9 ± 3 months in respectively ISD alone and ISD + triamcinolone (p=0.16). Both studies reported no complications related to ointment of triamcinolone [236, 237].

In a small (n=28) cohort with LS-related strictures, an intra-urethral steroid regimen was successful (no need for subsequent escalation of therapy) in 25 (89%) patients after a mean follow-up of 25 months [157]. This regimen consisted of applying clobetasol cream 0.05% as lubricant on a calibration device (10-16 Fr catheter or dilator) twice a day during a minimum of two months. As most of these patients further continued with instillation of steroids on a calibration device, this high "success" rate must be viewed with caution and should be considered as a stabilisation of the stricture rather than a cure. Eventually, twelve (42.8%) patients could reduce the interval of instillation/dilatation and three (10.7%) of them could finally stop the treatment [157].

Summary of evidence	**LE**
Stricture recurrence was reduced in men performing intermittent self-dilatation (ISD) versus those who did not.	1a
Intra-urethral corticosteroids in addition to ISD delays the time to recurrence.	1a

Recommendations	**Strength rating**
Perform intermittent self-dilatation (ISD) to stabilise the stricture after dilatation/direct vision internal urethrotomy if urethroplasty is not a viable option.	Weak
Use intra-urethral corticosteroids in addition to ISD to stabilise the urethral stricture.	Weak

6.2.3.2 Intralesional injections

The rationale of adjuvant intralesional injections is to reduce fibroblast proliferation and excessive urethral scaring [238].

6.2.3.2.1 Steroids

A 2014 SR identified five studies comparing intra-urethral submucosal steroid injection vs. no intra-urethral submucosal steroid injection after DVIU, of which two were RCTs [235]. Meta-analysis of these two RCTs with 57 and 58 patients in, respectively, the steroid and control group showed no statistical difference in recurrence rate (OR: 0.53; 95% CI: 0.25-1.13; p=0.10). Time to recurrence was significantly longer in the steroid group (weighted mean difference = 4.43; 95% CI: 2.77–6.09, p < 0.00001). There were no significant differences regarding adverse events (infection, bleeding, extravasation) between both groups (weighted mean difference = 1.59; 95% CI: 0.71–3.58, p=0.26).

6.2.3.2.2 Mitomycin C

In 2021 a SR and meta-analysis of different adjuncts to minimally invasive treatment of urethral stricture in men, mitomycin C (MMC) was associated with the lowest rate of urethral stricture recurrence (intralesional injection: OR 0.23, 95% CI 0.11-0.48; P<0.001; intraluminal injection: OR 0.11, 95% CI 0.02-0.61; P=0.01) [239]. Another SR and meta-analysis in 2021 from Xu *et al*., on the efficacy of MMC combined with direct vision internal urethrotomy, revealed that the effect of MMC was significant in short (≤ 2cm), anterior urethral strictures, in the longer (>12 months) follow-up group [240].

In the absence of well-conducted and adequately powered RCTs along with the lack of standardisation (dose, technique, volume, etc.) in the current literatue, carefull clinical review and prospective data collection as part of a clinical trial is advised.

6.2.3.2.3 Platelet rich plasma

Rezaei *et al*., conducted an RCT comparing DVIU + platelet rich plasma (PRP) (n=44) vs. DVIU + saline (n=43) in primary, bulbar strictures < 1.5 cm in length [241]. The two-year stricture-free rate was 78% vs. 56% after DVIU with or without PRP, respectively (p=0.034). Complications were frequent but not significantly different between both groups (DVIU + PRP: 70%; DVIU + saline: 79%). All complications (urethral bleeding, haematuria, urethral pain, pelvic pain, urinary leakage and genitoperineal swelling) were classified as grade 1 according to the Clavien-Dindo system. Further validation of this treatment is needed before general clinical implementation.

Summary of evidence	**LE**
Intralesional injections after direct vision internal urethrotomy (DVIU) might improve stricture-free rates on the short-term compared to DVIU alone. Experience is limited and the use of these drugs are off-label. Significant uncertainty exists about drug, dose, volume and technique.	1a

Recommendation	**Strength rating**
Use intralesional injections only in the confines of a clinical trial.	Weak

6.2.3.3 Urethral stents

Urethral stents are designed with the aim to oppose wound contraction after dilatation or DVIU [242, 243]. Stent insertion is a short procedure (< 60 minutes) that can be done under local or spinal anaesthesia as “oneday” surgery [242, 244, 245]. Urethral stents are classified as permanent or temporary (removable, after six to twelve months).

6.2.3.3.1 Results

Permanent stainless-steel mesh stents are no longer commercially available. An RCT comparing dilatation/DVIU only vs. dilatation/DVIU followed by temporary stent insertion for bulbar strictures reported a significantly longer stricture-free survival time in favour of dilation/DVIU followed by stent (median 292 vs. 84 days; p < 0.001) [246]. Only 20.6% of patients treated with a stent developed a recurrent stricture within one year vs. 82.8% in the control group. These results are corroborated by a prospective series of Wong *et al*., who found a median stricture-free survival of two months after DVIU alone vs. 23 months after DVIU followed by temporary (three months) stent for bulbar strictures [243].

Failure and need for re-intervention are frequent (30-53%) and are usually because of stricture recurrence, stent encrustation, stent migration and urethral hyperplasia. Other complications include recurrent UTI, recurrent haematuria and genito-perineal pain (Table 6.5). Although stents are mainly used to treat bulbar strictures, they have been used for posterior stenoses as well. Stents used in the posterior urethra have a high risk (82-100%) of causing UI and this is most pronounced in patients with previous irradiation and/or strictures extending into the membranous or bulbar urethra [247]. In the bulbar urethra, the risk of UI is higher if stent placement is adjacent to the external sphincter [248]. The use of stents in the penile urethra is anecdotal. Jung *et al*., reported stent failure in 4/7 (57%) patients with a penile stricture after a mean follow-up of eight months. Of those patients who failed, no patient with distal or pan-penile strictures was rendered stricture-free [249]. In their series, stricture recurrence after stenting of the penile urethra was significantly higher when compared to the bulbar urethra [249]. Although no direct comparison is available, temporary stents tend to have fewer and less severe complications compared to permanent stents (Table 6.7).

6.2.3.4 Drug-coated balloon dilatation

Drug (paclitaxel)-coated balloon dilatation (DCBD) after standard dilatation or DVIU aims to reduce scar formation based on its antimitotic action. The ROBUST-3 trial prospectively randomized patients with predominantly bulbar strictures (< 3cm length) and at least two prior failed endoscopic treatments to DCBD (n=79) or standard dilatation/DVIU (n=48) [250]. Anatomic patency (assessed by cystoscopy) at six months was 75% for DCBD versus 27% after standard dilatation/DVIU (p<0.001). Estimated one year-retreatment free survival was 83% versus 22% for respectively DCBD and standard dilatation/DVIU (p<0.001). There were no serious adverse events related to DCBD although patients undergoing DCBD had a higher rate of hematuria and dysuria compared to controls (11.4% versus 2.1%). Paclitaxel was detected in semen up to six months after treatment which urges for contraception if the partner has child-bearing potential. If used, careful clinical review and prospective data collection ideally part of a post marketing registry or clinical trial is advised.

Summary of evidence	LE
Drug (paclitaxel)-coated balloon dilatation is associated with higher anatomic patency rates (at six months) and lower risk of retreatment (at one year) as compared to standard dilatation/DVIU in patients with short (< 3 cm), bulbar strictures that underwent at least two prior failed endoscopic treatments.	1b

Recommendation	Strength rating
Offer drug (paclitaxel)-coated balloon dilatation for a short (< 3 cm) bulbar stricture recurring after at least two prior endoscopic treatments, but only in patients for whom urethroplasty is not an option.	Weak

6.2.3.4.1 Treatment of stent failure

In the case of stent failure, subsequent urethroplasty (usually with stent removal) is possible, but this urethroplasty is very likely to be more complex than it would have been had it been performed initially [251-253]. Due to the fact that the stainless-steel wires are fully embedded into the urethral wall, over time the urethral spongiosum is severely damaged. Horiguchi *et al*., found that a history of urethral stenting was an independent significant predictor of increased stricture complexity (OR: 13.7; 95% CI: 1.7-318.3; p=0.01) and need for more complex urethroplasty (OR: 6.9; 95% CI: 1.1-64.5; p=0.04) [234]. The majority (62%) of patients in this study had a permanent stent and tend to be difficult to remove because they are epithelialised, usually within six months [234]. The type of urethroplasty required depends on the length of the stricture and quality of local tissues [252]. In the majority of cases, it is possible to preserve the urethral plate and to perform a one-stage substitution urethroplasty [251, 252, 254]. The patency rates after different types of urethroplasty vary greatly between 16.7-100% [251-254] and this variation probably reflects variation in complexity of the stricture, rather than that the superiority of one technique of urethroplasty over another (for further information see supplementary Table S6.2). Due to these limitations, the use of stents should be avoided if subsequent urethroplasty is considered [242, 253]. Urethral stents are not a first-line treatment for urethral strictures but can be considered in co-morbid patients who have a recurrent stricture after DVIU/dilatation and are unable to have more complex urethroplasty or who refuse urethroplasty [242, 246, 247].

Summary of evidence	LE
Permanent urethral stents have a high complications and failure rate and make subsequent urethroplasty more challenging if they fail.	3
Stents have a higher failure rate in the penile urethra.	3
Temporary stents after DVIU (direct vision internal urethrotomy) /dilatation at the bulbar urethra prolong time to next recurrence compared to DVIU/dilatation alone.	1b

Recommendations	Strength rating
Do not use permanent urethral stents.	Strong
Do not use urethral stents for penile strictures.	Strong
Use a temporary stent for recurrent bulbar strictures after direct vision internal urethrotomy to prolong time to next recurrence only if urethroplasty is not a viable option.	Weak

Table 6.5: Failure rate and complications associated with urethral stents

Study	Type of stent	Duration	N	FU (months)	Stricture length (cm)	Stricture location	Previous interventions	Failure rate	Defintion failure	Complications						
										UTI	haematuria	stent encrustation/ stone formation	stent migration	urethral hyper-plasia	Local pain	UI
Abdallah *et al*. [242]	Thermo-expandable nitinol	Temporary	23	17 (6)	3.6 (1.2)	Bulbar	DVIU/ urethroplasty: all	12 (52%)	Need for re-intervention	4 (17%)	3 (13%)	3 (13%)	5 (22%)	2 (8%)	6 (26%)	NR
Jordan *et al*. [246]	Thermo-expandable nitinol	Temporary	63	12	2.7 (1.6)	Bulbar	DVIU only: all	28 (44%)	Inability to pass 16 Fr cystoscope	31 (49%)	10 (16%)	3 (4.7%)	8 (13%)	NR	19 (30%)	12 (19%)
Temeltas *et al*. [245]	Polymer-coated	Temporary	28	29 (7-46)	1.9 (0.5-3.5)	Bulbar	DVIU only: all	10 (36%)	Stricture recurrence on urethroscopy/ graphy, Q_{max} < 15 ml/s, UTI	NR	NR	1 (3.6%)	3 (11%)	NR	0 (0%)	NR
Wong *et al*. [243]	Thermo-expandable nitinol	Temporary	22	23 (9-31)	2.4 (1-4.5)	Bulbar	DVIU only: all	7 (32%)	Inability to pass 17 Fr cystoscope, Q_{max} < 10 ml/s or recurrent obstructive symptoms	0 (0%)	NR	0 (0%)	1 (4.5%)	0 (0%)	0 (0%)	NR
Atesci *et al*. [244]	Thermo-expandable nitinol	Permanent	20	144 (120 -192)	2.5 (0.5-5.5)	Bulbar	DVIU/ urethroplasty: all	6 (30%)	Need for re-intervention	NR	NR	4 (20%)	2 (10%)	0 (0%)	8 (40%)	1 (5%)
Sertcelik *et al*. [248]	Thermo-expandable nitinol	Permanent	47	101 (84-125)	2 (0.5-5)	Bulbar (45), bulbomem-branous (2)	urethroplasty (19%)/ DVIU (64%)/ railroading (17%)	22 (47%)	Need for re-intervention	NR	NR	12 (26%)	2 (4%)	7 (15%)	20 (43%)	9 (19%)
Erickson *et al*. [247]	Self-expandable super alloy mesh	Permanent	38	28 (30)	3 (1.7)	Posterior (prostate cancer related); VAUS 24; prostatic urethra (irradition) 14	DVIU only: all	20 (53%)	Need for re-intervention	7 (18%)	3 (8%)	6 (16%)	NR	NR	6 (16%)	31 (82%)

DVIU = direct vision internal urethrotomy; FU = follow-up; NR = not reported; UI = urinary incontinence; UTI = urinary tract infection; VUAS = vesico-urethral anastomotic stricture; Q_{max}= maximum flow rate

6.3 Open repairs (urethroplasty): site and aetiology (clinical scenario) treatment options

6.3.1 The role of urethroplasty in the management of penile urethral strictures

Due to the specific aetiology and the associated problems, strictures related to failed hypospadias repair and LS will be discussed separately. However, many series reporting on the outcome of penile strictures have a mixed aetiology also including failed hypospadias repair and/or LS [255, 256]. Due to their specific location, distal penile strictures will be discussed separately.

6.3.1.1 Staged augmentation urethroplasty

Classically called "two-stage" urethroplasty, this approach may become a multi-stage urethroplasty as revision (usually due to graft contracture) after the first stage has been reported in 0-20% of cases [256-259]. Therefore, the term "staged" should be used instead [260]. Revision rates before second stage were 0-20%, stressing that a two-stage urethroplasty might become a multi-stage urethroplasty. In general, reconstructive urologists tend to follow this approach in men with more complex urethral stricture disease (multiple interventions in the past, unfavourable clinical findings such as significant spongiofibrosis or scarring that requires excision, poor quality of the urethral plate). An interval of at least four to six months has been proposed before proceeding to the tubularisation of the urethra, provided that the graft has healed uneventfully [261-263].

A SR by Mangera *et al*., has shown an average patency rate of 90.5% with the use of all types of grafts for staged penile urethroplasties with an average follow-up of 22.2 months [264]. Patency rates of staged oral mucosa graft (OMG) urethroplasty in specific locations vary between 73.3 and 100% [255, 256, 258, 259, 265, 266]. Post-operative urethrocutaneous fistula (UCF) rates were 17.2% and 2.6% in the studies of Ekerhult *et al*., and Joshi *et al*., respectively, and either not reported or unclear in the remaining studies [255, 256].

6.3.1.2 Single-stage augmentation urethroplasty

Single-stage urethroplasty offers the option for reconstruction of the stricture without the need for multiple operations, the associated peri-procedural risks, and the cosmetic and functional implications that by definition follow the first part of staged urethroplasties [267-269]. There is some evidence to suggest a considerable number of patients (50% or more in some studies) who were offered first stage urethroplasty never returned for the second stage because they were either satisfied with their functional status after the first stage (this particularly applied to older men or patients with multiple failed procedures in the past) or they were disappointed with the need for another operation [267, 268].

In the SR of Mangera *et al*., overall patency rate for all types of single-staged graft urethroplasties is 75.7% with an average follow-up of 32.8 months [264].

The patency rate for different one-stage techniques in particular are:

- dorsal OMG (n=320): 63-100% [265, 266, 259, 270-276];
- ventral OMG (n=54): 55-92.6% [265, 277, 278];
- double (dorsal + ventral) onlay with penile/scrotal skin graft /OMG (n=14/8/4): 88.5% [272];
- dorsal penile skin graft (n=44): 62-78% [272, 273];
- penile skin flap (n=367): 67-100% [265, 266, 272-274, 279].

No high-level evidence exists to state that one technique is superior to another, but it seems that the dorsal graft location is more commonly used compared to the ventral one. Mangera *et al*., reported that the patency rate was better with OMG compared to other grafts (mainly penile skin) [264]. Jiang *et al*., showed that combined (dorsal + ventral) BMG onlay had significantly better stricture-free rates for penoscrotal strictures (patency rate 88.9% vs. 60.9% with single-onlay approach); however, follow-up was significantly shorter in the double-onlay group [280]. Few studies have reported dedicated results on sexual function parameters that do not appear to be significantly impaired post-operatively [258, 281].

A critical factor with respect to single-staged procedures is the careful selection of patients, as men with long and complex strictures might not be good candidates for single-stage reconstruction and attempts to offer single-staged operations in these patients might lead to higher recurrence rates. Sometimes, this selection can only be done based on intra-operative findings. Therefore, any scheduled single-staged procedure might be converted into a staged one [267, 282]. Palminteri *et al*., highlighted the fact that single-stage augmentation urethroplasties in men with LS-related strictures enlarge rather than remove the diseased segment of the urethra; therefore, there is always a risk of recurrence in the future [283]. The role of previous interventions (especially multiple urethrotomies or history of previous urethroplasties) remains unclear as several studies on single-staged operations do not provide information on previous procedures, or excluded patients with operations in the past [274, 281]. Although favourable outcomes in patients with previous history

of urethrotomies/urethroplasties were reported by Barbagli and Kulkarni, in the study by Pfalzgraf *et al*., all recurrences post-previous urethroplasty took place in the single-stage group while Ekerhult *et al*., identified prior history of urethral operations as a risk factor for recurrence in the group of single-stage procedures [255, 258, 259, 272]. In addition to previous urethral surgery, high BMI has also been identified as a poor prognostic factor after single-stage penile urethroplasty [255].

6.3.1.3 Anastomotic urethroplasty in men with penile urethral strictures

Historically, the use of anastomotic urethroplasty in the management of urethral stricture disease has been discouraged due to the risk of chordee post-operatively [263, 284]. Nevertheless, it has been performed in selected patients with very short strictures (usually < 1 cm) with 80-93% patency rate, with satisfactory QoL and sexual function and without any case of chordee [285] and with results comparable to augmentation urethroplasty [286].

Summary of evidence	**LE**
Stricture-free rates for single-stage penile augmentation urethroplasties range from 70%-100% for dorsal OMG augmentation, 67-100% for penile skin flap (PSF) augmentation, 55-92.6% for ventral OMG augmentation and 62-78% for dorsal SG augmentation. Overall stricture-free rates for staged OMG penile augmentation urethroplasties range from 70-100%.	2b
In staged urethroplasties, an interval of at least four to six months has been proposed before proceeding to the tubularisation of the urethra, provided that the graft has healed uneventfully.	4
The use of anastomotic urethroplasty in the management of urethral stricture disease has been discouraged due to the risk of chordee post-operatively. Anastomotic urethroplasty can be offered in selected cases of very short (< 1 cm), injury-associated penile strictures.	3
In case of adverse intra-operative findings, a single-stage approach might not be feasible and must be converted into a staged approach.	3

Recommendations	**Strength rating**
Offer men with penile urethral stricture disease augmentation urethroplasty by either a single-stage or staged approach taking into consideration previous interventions and stricture characteristics.	Strong
Offer an interval of at least four to six months before proceeding to the second stage of the procedure provided that outcome of the first stage is satisfactory.	Weak
Do not offer anastomotic urethroplasty to patients with penile strictures > 1 cm due to the risk of penile chordee post-operatively.	Strong
Counsel patients with penile strictures that single-stage procedures might be converted to staged ones in the face of adverse intra-operative findings.	Strong

6.3.1.4 Specific considerations for failed hypospadias repair-related strictures

The term "failed hypospadias repair" (FHR) includes a wide range of abnormalities after previous attempts for reconstruction, such as glans deformity, recurrent urethral stricture, glans/urethral dehiscence, UCF and penile chordee [287-289]. The management of FHR is challenging as the urethral plate, penile skin and dartos fascia are often deficient/non-existent. Management of these patients is often made more difficult due to incomplete health records and a lack of critical information (original meatal site, number, and type of previous repairs) [261, 290]. In addition, multiple operations might need to be offered to reach satisfactory outcomes [287]. As a result, FHR should always be considered as a complex condition and it is advised that FHR management takes place in high-volume centres [288, 289, 291, 292].

"Hypospadias cripples" is a term widely used to describe the group of men with multiple previous failed attempts to correct the condition resulting in unfavourable results such as severe scarring, penile deformity and shortening, hair or stones in the urethra, UCF, chordee and functional disorders (e.g., urinary, or sexual dysfunction). This term should be avoided and a more neutral one should replace it as it further stigmatises men with hypospadias who have been shown to have reduced self-esteem and confidence due to unsatisfactory cosmesis, and problematic urinary and sexual function. Moreover, it has been reported that FHR patients experience high rates of disappointment after failure of attempted repair and a sense of helplessness as they are frequently advised that their failed hypospadias is too complex to correct and they should not pursue further repair [288-290, 293, 294].

Two main approaches are applicable: single-stage or staged procedures. In general, it is advised that staged procedures should be followed when the urethral plate is inadequate for a single-stage operation. Surgeons should consent patients for both types of urethroplasty as the surgical approach might need to be modified intra-operatively depending on favourable/unfavourable intra-operative findings. Besides poor-quality of the urethral plate, these unfavourable findings include high degree of scarring and presence of concomitant LS, UCF and/or chordee. It is not uncommon for men with FHR to have scarred skin or concurrent LS and thus, skin grafts or flaps should be avoided as the risk of recurrence due to LS is very high (90% in long-term follow-up as reported by Depasquale *et al*.) [39, 295, 296].

Staged repairs (using mainly BMG) reported patency rates ranging from 71-95% [293, 295, 257, 297, 298], while single-stage repairs had patency rates from 80-100% [295, 297, 299-302]. It needs to be highlighted that, as FHR is an umbrella term that covers various clinical conditions apart from urethral stricture disease only (such as UCF, chordee, penile deformity), "success" rates as reported by the authors in their studies do not represent urethral patency rates only. Unfortunately, the number of previous operations is either not reported or refers to the whole FHR study group collectively rather than to the subgroups of staged/single-staged procedures.

A comparative analysis is reported by Barbagli *et al*., in 345 FHR patients at five-year follow-up. Overall failure-free survival rate was 48% for all urethroplasties, and in sub-analysis, staged techniques had significantly lower treatment failure-free survival rates compared to single-stage techniques [303]. However, it is unclear whether these groups were comparable in terms of baseline characteristics such as age, length of stricture, number of procedures, comorbidities etc. [303]. If the patients in the staged group had a more unfavourable background, this on its own could explain the final outcome rather than the surgical approach itself.

Kozinn *et al*., reported a 16% and 14% revision rate after the first and second stage, respectively, and observed that these revision rates were higher in the FHR group compared to non-FHR patients with penile strictures [257]. There is conflicting evidence whether FHR as aetiology is a poor prognostic factor in the outcome of urethroplasty for penile strictures [255, 304-306]. Concomitant UCF can be successfully managed at the same time of urethroplasty [303].

Saavendra *et al*., reported 89.3% stricture-free rate in 56 FHR patients with penile urethral strictures at a median of 21 months follow-up using mainly staged urethroplasty and perineal urethrostomy. Verla *et al*., presented departmental experience with the use of various urethroplasty techniques in a total of 76 FHR patients with penile strictures. Follow-up was long, at a median of 89 months and stricture-free rates ranged from 29% (anastomotic repair) to 90% first stage only of multistage urethroplasty).

For further information see supplementary Table S6.3.

Summary of evidence	**LE**
Men with failed hypospadias repair (FHR) have history of multiple interventions, and poor-quality tissues, and might require complex procedures for a satisfactory functional and cosmetic outcome.	4
Men with FHR may have low self-esteem due to urinary and sexual dysfunction and unsatisfactory cosmesis.	2b
Men with FHR can have scarred penile skin or concurrent lichen sclerosus and outcomes with skin grafts or flaps can be unsatisfactory.	3

Recommendations	**Strength rating**
Men with failed hypospadias repair (FHR) should be considered complex patients and referred to specialist centres for further management.	Weak
Propose psychological and/or psychosexual counselling to men with unsatisfactory cosmesis and sexual or urinary dysfunction related to FHR.	Weak
Do not use penile skin grafts or flaps in failed FHR patients with lichen sclerosus or scarred skin.	Strong

6.3.1.5 Specific considerations for lichen sclerosus-related penile urethral strictures

Given the fact that LS affects the skin, the use of genital skin as a flap or graft is not advised as the risk of disease recurrence has been reported to be high (50-100%) and while most of recurrences tend to occur within the first two to three post-operative years, late recurrences have been reported [307].

Main strategies are single-stage or staged oral mucosa graft urethroplasty.

The EAU Urethral Strictures Guidelines Panel conducted a SR [6] to explore the role of single-stage oral mucosa graft urethroplasty in the management of LS-related urethral strictures and to compare its outcomes with alternative management options (surgical dilatations +/- ISD; surgical dilatations + local steroids +/- ISD; staged oral mucosa urethroplasty; penile skin urethroplasty; meatotomy/meatoplasty; urethrotomy [Otis, DVIU]; perineal urethrostomy; urinary diversion [e.g., suprapubic catheterisation]).

In total, fifteen studies met the inclusion criteria, recruiting a total of 649 patients (366 from five non randomised comparative studies and 283 from ten, single-arm retrospective observational studies). Singlestage OMG urethroplasty resulted in success rates ranging from 65-100% after twelve to 67 months mean or median follow-up. For staged OMG urethroplasty, the most commonly reported comparator, the success rates were somewhat lower and varied between 60-79%. Methodological issues (mainly selection bias) could explain the difference in success rates rather than the intervention itself. Complications were uncommon (0-12%) and mainly comprised Grade 1-3 events.

Due to the overall very poor quality of evidence, the SR did not provide a clear answer as to whether singlestage OMG urethroplasty is superior to other management options, although careful patient selection is highlighted. In the absence of adverse local tissue conditions, a single-stage approach could lead to high success rates with an improvement in voiding symptoms and QoL.

Summary of evidence	**LE**
Lichen sclerosus is a skin condition that can lead to scarring, and recurrence rates after skin graft/flap augmentation urethroplasties have been reported to be high (50-100%).	4
Single-stage oral mucosa graft (OMG) urethroplasty provides patency rates between 65 and 100% and is not inferior to staged OMG urethroplasty.	3

Recommendations	**Strength rating**
Do not use genital skin in augmentation penile urethroplasty in men with lichen sclerosus (LS) related strictures.	Strong
Perform single-stage oral mucosa graft urethroplasty in the absence of adverse local conditions in men with LS related strictures.	Weak

6.3.1.6 Distal urethral strictures (meatal stenosis, fossa navicularis strictures)

Open repair of distal urethral strictures can be in the form of Malone meatoplasty, skin flap meatoplasty or graft (skin [SG]/OMG) urethroplasty.

For short distal meatal strictures, the Malone meatoplasty (dorsal + ventral meatotomy) provides a technique with patency rates up to 100%, and 83% patient-reported satisfaction with the cosmetic results [308]. Similarly, Hofer *et al*., presented their technique variation (ventral excision of scar and eversion of the urethral mucosa) and showed 81% stricture-free rates at 41-month mean follow-up.

Skin flap meatoplasty showed excellent patency rates ranging from 90-96% based on three studies comprising 67 patients [309-311]. In addition, based on their results, patient satisfaction with post-operative outcomes and cosmesis was high, there were no cases of ED and functional complaints were minimal (mainly spraying of the urine flow).

Patency rates with the use of grafts (OMG or SG) ranged from 69-91% in 106 patients overall [312, 313, 300]. Where reported, patients were satisfied with cosmesis, and mild spraying of the urine flow self-resolved. Although tubularised grafts in a single-stage procedures are not routinely recommended (see also section 9. Tissue transfer), one series reported an 89.9% patency rate for this approach ("two-in one approach") in selected patients with mainly distal penile strictures [314].

Finally, Daneshvar *et al*., presented a novel transurethral ventral inlay OMG technique and showed excellent stricture-free rates (96%) at short follow-up though (median 16 months).

For further information see supplementary Table S6.4.

Summary of evidence	LE
Post-meatoplasty/urethroplasty patency rates in men with meatal stenosis or fossa navicularis/distal urethral strictures range between 57-100% depending on type of surgical intervention with high patient satisfaction and minimal complications.	3

Recommendation	Strength rating
Offer open meatoplasty or distal urethroplasty to patients with meatal stenosis or fossa navicularis/distal urethral strictures.	Weak

*6.3.2 **Urethroplasty for bulbar strictures***

6.3.2.1 "Short" bulbar strictures

The length of a "short" bulbar stricture is poorly defined. In general, "short bulbar strictures" are those amenable to stricture excision and subsequent tension-free anastomotic repair. The limit is usually around 2 cm [315].

In fit patients, the choice of urethroplasty is between EPA (transecting or non-transecting) and FGU.

6.3.2.1.1 Excision and primary anastomosis

6.3.2.1.1.1 Excision and primary anastomosis with transection of corpus spongiosum (transecting EPA)

Transecting EPA (tEPA) is based on the full thickness resection of the segment of the bulbar urethra where the stricture and surrounding spongiofibrosis is located. Reconstruction is performed by a tension-free spatulated anastomosis.

6.3.2.1.1.1.1 Patency rates

The International Consultation on Urological Diseases (ICUD) performed an extensive review of the literature and reported a composite patency rate of 93.8% for tEPA [316]. Based on this, they endorsed tEPA as treatment of choice for short bulbar strictures if other techniques have an expected patency rate below 90%. However, penile complicationswere not taken into account for this advice and as discussed below, these are a concern with tEPA.

Prospective data report a patency rate of 88% at twelve months follow-up [315].

Usually, no need for further intervention is used to evidence that the urethra is patent. In the few studies using an anatomic definition for failure (an inability to pass a 16 Fr endoscope) tEPA urethroplasty achieves a similar patency rate, ranging between 85.5-97% [145, 317-319] (Table 6.12). The median time for recurrence after tEPA is between 3.5 and thirteen months [145, 320, 321].

Several authors suggested that tEPA is the technique of choice for short post-traumatic bulbar strictures with complete obliteration of the urethral lumen and full thickness spongiofibrosis [319, 322]. These strictures are a specific entity and usually the result of a straddle injury with complete or nearly complete rupture of the bulbar urethra. These obliterations are predominantly short and can be treated with tEPA yielding a patency rate of 98.5% as reported in the series of Horiguchi *et al*., [323]. They also reported an improvement in erectile function after urethroplasty measured one year post-operatively. Straddle injury (and perineal trauma) are a common aetiology in papers published about tEPA; however, separate data on the outcomes for this specific aetiology is usually lacking.

6.3.2.1.1.2 Complications

Nilsen *et al*., conducted an RCT comparing tEPA with FGU for short (< 2 cm) bulbar strictures [315]. Compared to FGU, penile complications were more frequent with tEPA. After three months, worse ejaculation (26%), reduced glans filling (26%), penile shortening (16%) and penile chordee (10%) were significantly more reported with tEPA. After 12 months, reduced glans filling (19%) and penile shortening (26%) remained significantly more reported with tEPA. A scrotoperineal hematoma was significantly more frequent with tEPA compared to FGU (resp. 24 versus 4%). Despite these complications IIEF-5 was not significantly different between both groups at three and twelve months.

These latter complications (as well as ED) might be attributed to complete transection of the corpus spongiosum at the level of the stricture, thereby disrupting the antegrade blood flow of the urethra and corpus spongiosum. To spare this, the non-transecting EPA (ntEPA) has been described [324] and later modified [325].

6.3.2.1.1.2 Non-transecting excision and primary anastomosis

6.3.2.1.1.2.1 Patency rates

Except for straddle injuries that are usually associated with complete obliteration of the lumen and full thickness scarring of the corpus spongiosum [319, 326], ntEPA is a good alternative for short bulbar strictures of all other aetiologies. With median follow-ups ranging between 17.6 and 37.1 months, the patency rates reported are 93.2-99%; with the lack of further intervention as success criteria [322, 327, 328]. Even with the anatomic criteria (16 Fr cystoscopy passage) the success rate achieved was 97.9% at twelve months [319] (see supplementary Table S6.7).

Two comparative analyses evaluated tEPA vs. ntEPA. Waterloos *et al*., reported patency rates of 88.4% and 93.2%, respectively, for tEPA and ntEPA (p=0.33) but with significantly longer follow-up for tEPA (118 vs. 32 months, p < 0.001). Of patients scheduled for ntEPA, 11.1% were converted to tEPA, highlighting that ntEPA is not always possible. Chapman *et al*., using anatomic success criteria (16 Fr cystoscope passage), reported patency in 93.8% of tEPA vs. 97.9% of ntEPA. Follow-up was also significantly shorter at 74.1 (SD: 45.4) months for tEPA vs. 37.1 (SD: 20.5) months for ntEPA (p < 0.001) [319].

6.3.2.1.1.2.2 Complications

When erectile function after urethroplasty was assessed (at six months), ntEPA had significantly lower ED rates (a decrease of > 5 points on the sexual health inventory for men [SHIM] scale) compared to tEPA (4.3 vs. 14.3%, respectively) [319]. Urethral transection performed during tEPA was the only factor associated with sexual dysfunction in a multivariate analysis [319]. Other series reported ED lasting for more than six months in 2-6% of cases after ntEPA [322, 328, 329]. Grade > 2 Clavian-Dindo complications were 3.6-8.1% vs. 4.3-6.8%, respectively, for tEPA and ntEPA, without reaching statistical significance [319, 327].

To date, no trials comparing ntEPA with FGU have been published to report on comparative patency outcomes and complications.

6.3.2.1.2 Free graft urethroplasty

Despite the very high patency rates of EPA, FGU has been performed for short bulbar strictures as well. This is mainly driven by reports of ED after EPA. A meta-analysis of ten papers [340] comparing tEPA with BMG FGU for short strictures, found that tEPA is better than BMG FGU in terms of patency rates (91.5% vs. 70%), whilst BMG FGU has less erectile complications (9% vs. 25%). However, the methodology of this meta-analysis must be disputed as it was performed on cohort studies without risk of bias assessment and without further specification of timing of assessment of ED. On the other hand an RCT comparing tEPA with BMG FGU, found no significantly different patency rates for EPA compared to BMG FGU (88% versus 87% respectively) and no significant differences in erectile function for tEPA compared to BMG FGU [315]. As mentioned earlier, penile complications were more frequent with EPA.

Dogra *et al*., [283] looked prospectively at sexual function in 87 patients after different urethroplasties (EPA, penile/bulbar substitution) and found a 20% reduction in sexual function in all groups, which resolved after six months.

Details on where to place the graft during FGU are discussed below.

Summary of evidence	**LE**
For short post-traumatic strictures tEPA has good patency rates.	3
For short bulbar strictures not related to straddle injury tEPA, ntEPA and FGU have the same patency rates, but ntEPA and FGU have less erectile dysfunction or penile complications than tEPA.	1b-3*

**LE1b for comparison between tEPA and FGU and LE3 for tEPA versus ntEPA versus FGU*

Recommendations	Strength rating
Use transecting excision and primary anastomosis (tEPA) for short posttraumatic bulbar strictures with (nearly) complete obliteration of the lumen and full thickness spongiofibrosis.	Strong
Use non-transecting excision and primary anastomosis or free graft urethroplasty instead of tEPA for short bulbar strictures not related to straddle injury.	Weak

6.3.2.2 "Longer" bulbar strictures

6.3.2.2.1 Free graft urethroplasty

For strictures not amenable to EPA, FGU is the technique of choice and buccal mucosa is, at the moment, the most widely used graft. Other grafts (and flaps) are possible and discussed in the tissue transfer chapter. Patency rates of FGU of the bulbar urethra are 88-91% with twelve to 40 months follow-up [264, 330]. There is a suggestion that patency rates deteriorate with time [331].

During bulbar urethroplasty, the bulbospongiosus muscle is usually separated at the midline which may cause damage to the muscle and perineal nerves. This might subsequently provoke post-void dribbling and ejaculation disorders. In order to reduce this, the muscle and nerve-sparing perineal approach has been introduced [332]. Although it is mostly used in graft urethroplasty, this approach is also possible for EPA [333]. Elkady *et al*., [329] randomised 50 patients between a muscle and nerve-sparing perineal approach vs. a classic perineal approach and found no difference in operative time (100 vs. 105 min), but significantly less dribbling (4% vs. 36%, p=0.01), and significantly less ejaculatory changes (8% vs. 40%, p=0.02) in the nerve and muscle-sparing group. Fredrick *et al*., [333] did the same in 50 patients in a multicentric study with bulbar urethroplasty but could not find a statistical difference regarding post-void dribbling and ejaculatory changes. Due to the limited and conflicting evidence, no recommendation can be made about the routine use of nerve and muscle-sparing modification during bulbar urethroplasty.

See supplementary Table S6.8 for further information.

6.3.2.2.2 Augmented anastomotic repair

Augmented anastomotic repair has been described for these strictures. It has been mainly performed in cases where the stricture was just too long (+/- 2-4 cm) for tension-free EPA [334]. It can also be performed for longer strictures with a shorter (nearly) obliterative segment [335]. In this case, only the most obliterative segment is excised, the urethral plate is anastomosed, and the urethra is further reconstructed with an onlay graft [335]. Patency rates after AAR vary between 91.1 - 91.9% with twelve to 28 months follow-up [334]. The use of this technique has been challenged by Redmond *et al*., who found a 4.8 higher risk of recurrence when AAR was used compared to (dorsal) free graft urethroplasty [336] (see supplementary Table S6.9).

A non-transecting alternative has also been described to overcome the previously mentioned inconveniences related to spongiosal transection (augmented non-transecting anastomotic bulbar urethroplasty [ANTABU]). With this technique, Bugeja *et al*., [337] reported a 100% patency rate in sixteen patients after a median follow-up of thirteen months. One patient (6.7%) suffered permanent ED.

Summary of evidence	LE
For strictures not amenable to EPA, FGU provides an 88-91% patency rate at short to medium follow-up	1b
Augmented anastomotic repair provides good (88-92%) patency rates for bulbar strictures with a nearly obliterative segment, despite deterioration with time.	3

Recommendations	Strength rating
Use free graft urethroplasty for bulbar strictures not amendable to excision and primary anastomosis (EPA).	Strong
Use augmented anastomotic repair for bulbar strictures not amenable to EPA but with a short, nearly obliterative segment within the whole strictured segment.	Weak

6.3.2.2.3 Location of the graft during urethroplasty for bulbar strictures

The best location for graft positioning into the bulbar urethra remains to be determined. There are many techniques described with ventral, lateral, dorsolateral, or dorsal graft as an onlay or an inlay. Onlay means from the outside onto the urethra, inlay means from the inside after opening the urethra.

Regarding the site of graft placement, the Panel has conducted a SR assessing the literature from 1996 onwards, including studies with at least 20 patients and a minimum of twelve months follow-up [7]. This yielded one RCT, four non-randomised comparative series and 36 case series comprising 3,683 patients. The RCT of Vasudeva *et al*., compared ventral (n=40) with dorsal (n=40) onlay BMG urethroplasty and reported a patency rate of 90 - 92.5%, respectively at twelve months follow-up (p=0.51) [330]. The non-randomised comparative studies could not identify any significant differences in patency rates for dorsal onlay vs. ventral onlay, dorsal inlay vs. ventral onlay or dorsal onlay vs. ventral onlay vs. dorsolateral onlay. Case series reported a patency rate of 62.1-98.3% for dorsal onlay, 74.3-94.4% for ventral onlay and 78.4-92% for dorsal inlay. There are no arguments to assume a higher risk of ED with one of the four techniques. Post-void-dribbling was reported in 0-28.1% with dorsal onlay and in 20-21% with ventral onlay. Other complications were also similar in incidence between techniques. Urethrocutaneous fistula and urethral diverticulum were only reported with the ventral onlay technique although this consisted of only two and one cases, respectively.

Double ventral-dorsal onlay, proposed for high-grade/nearly obliterative strictures, yielded a patency rate of 90-91% after 22-33 months follow-up [146, 338].

Summary of evidence	**LE**
Location of the graft has no impact on patency rates.	1b

Recommendation	**Strength rating**
Use dorsal, dorsal-lateral, or ventral approach according to surgical practice, expertise, and intra-operative findings.	Strong

6.3.2.3 Staged urethroplasty for bulbar urethral strictures

6.3.2.3.1 Indications

Staged urethroplasty may be considered when:

- there are locally adverse conditions such as fistula, false passage, abscess, cancer [282, 339, 340];
- there has been a previously unsuccessful complex urethroplasty including failed hypospadias repair [257, 339];
- there is a lack of certainty on behalf of the surgeon regarding the most appropriate form of urethroplasty for the patient [339];
- the stricture is radiotherapy induced [257];
- the stricture is consequent to LS [257] (this is controversial and for some groups LS is a contraindication for a staged urethroplasty [305]; Kozinn *et al*., recommend leaving at least ten months between 1st stage and 2nd stage re-tubularisation in patients with LS to allow graft complication to develop) [257];
- there is severe spongiofibrosis [341].

6.3.2.3.2 Outcomes

Patency rates of 33.3-94.6% at mean follow-up of 11.2-50 months have been described for staged urethroplasty in series which include men with bulbar urethral stricture disease [257, 305, 318, 341-343]. Grafts (mesh graft, preputial skin, oral mucosa) can be used in staged augmentation as well as marsupialisation [318, 341]. In patients affected by LS, a 52.2% patency rate for staged urethroplasty was reported whereas this was 86% for single-stage buccal mucosa urethroplasty ($p < 0.01$) [305]. It is highly likely that different stricture and patient characteristics contributed to the differences reported and this should be kept in mind when interpreting the data. Of note, 19-45.5% of patients planned for staged urethroplasty declined to proceed to 2nd stage re-tubularisation [257, 342].

Early complications after staged procedures include wound dehiscence, UTI, epididymitis, scrotal abscess, and penile numbness. Specific to 2nd stage Johanson urethroplasty UCF occurs in 3-15%. The actual incidence of UCF is probably higher as many small fistulae close spontaneously with conservative management and are not formally reported [305, 318, 341].

Late complications of 1st stage urethroplasty include a need for revision in up to 19% - as a consequence of recurrence of LS in graft(s) (8.8%), graft contracture (6.6%) and stomal stenosis (3.3%) [257]. Late complications of 2nd stage urethroplasty include post-micturition dribble in 14-18%, SUI in up to 16%, penile curvature in up to 9%, ED in up to 4%, urethral diverticulum formation in 1% and cold glans [305, 341, 343]. Stress urinary incontinence, penile curvature and ED appear to be particularly associated with mesh graft stage urethroplasty [341, 343].

After their procedure, 86% and 96.6% of men with, respectively, mesh graft and buccal mucosa graft staged urethroplasty were satisfied. The patient groups included in the review were too small to detect significant differences [341]. All are retrospective series – with heterogenous indications, stricture locations (not exclusively bulbar), stricture lengths and patient groups. It is consequently difficult to draw meaningful conclusions from the little data that are available.

See supplementary Table S6.10 for more information.

Summary of evidence	LE
Staged urethroplasty for bulbar strictures and for strictures involving the bulbar urethra yields patency rates of 33.3-90% depending upon patient and stricture characteristics and patient satisfaction is high with all types of staged urethroplasty.	3
Lichen sclerosus is a relative contraindication for staged urethroplasty in the literature with lower long-term urethral patency rates of 52.2% compared to urethral patency rates of 64.3% in non-lichen sclerosis patients.	3
Up to 45.5% of men elect not to proceed to 2nd stage re-tubularisation after successful 1st stage.	3
Up to 19% of men required revision of their 1st stage urethroplasty.	3

Recommendations	Strength rating
Offer staged urethroplasty to men with complex anterior urethral stricture disease not suitable for single stage urethroplasty and who are fit for reconstruction.	Weak
Do not perform staged bulbar urethroplasty for lichen sclerosis if single stage urethroplasty is possible.	Weak
Consider staged procedure in patients unsure about perineal urethrostomy versus urethral reconstruction.	Weak
Warn men that staged urethroplasty may comprise more than two stages.	Weak

6.3.2.3.3 Risk factors

There is a lot effort in identifying risk factors affecting the success rate of urethroplasties.

The evidence is not clear about age, obesity, aetiology or prior radiation or prior surgery. The only clear risk factors in multivariate analysis are the length and the site of the stricture, success rates are better in shorter or bulbar strictures and worse in longer or penile strictures [317, 344-346]. Patient should be informed about the higher risk in longer and penile strictures.

6.3.2.3.4 Risk factors for adverse outcomes

In four series specifically dedicated to risk factors for failure after urethroplasty using multivariate analysis, there is conflicting evidence about several factors (aetiology, comorbidity, stricture length, prior therapy) that might be predictive for failure after urethroplasty (Table 6.6). Advanced age does not appear to be a risk factor for urethroplasty failure in the majority of studies, with the exception of Viers *et al*., 2017 [347] retrospective case series which found that the risk for recurrence was significantly higher beyond the age of 60 (< 50 yrs 94%, > 70 yrs 74%) in 184 patients having a wide variety of urethroplasties. Previous radiation therapy was also found to be a risk factor for stricture recurrence in both Viers' [347] retrospective case series and Ahyai's 2015 series [348] – with only a 71% patency rate at a median follow-up of 29 months in those with previous radiotherapy. Based on these data, a clear and evidence-based recommendation cannot be formulated.

Table 6.6: Risk factors for failure after urethroplasty based on multivariable Cox regression analyses

Study	N	Population	Comorbidity HR (95% CI)	Length HR (95% CI)	Aetiology HR (95% CI)	Prior stricture therapy HR (95% CI)
Breyer *et al*. 2010 [349]	443	Mixed	NS	NS	NS	Prior DVIU: 1.7 (1.0-3.0) Prior urethroplasty: 1.8 (1.1-3.1)

Kinnaird *et al.* 2014 [350]	604	Mixed	NS	≥ 5 cm: 2.3 (1.2-4.5)	Iatrogenic: 3.4 (1.2-10.0) LS: 5.9 (2.1-16.5) Infectious: 7.3 (2.3-23.7)	NS
Chapman *et al.* 2017 [317]	596	Isolated bulbar strictures	Overall comorbidity: 2.4 (1.1-5.3) Obesity: 2.9 (1.3-6.5)	1.2 (1.1-1.3)	Infectious: 3.7 (1.3-10.6)	NS
Verla *et al.* 2020 [351]	474	Anterior strictures	NS	NS	NS	NS

CI = confidence interval; HR = hazard ratio; LS = lichen sclerosus; N = number of patients; NR = not reported NS = not significant.

6.3.2.4 Management of recurrence after bulbar urethroplasty

Kahokehr *et al*., [334] followed nearly 400 patients after urethroplasty and found a recurrence rate of 6% (n=25). Ninety-two percent of the failed cases were treated successfully with DVIU and only 8% needed another open reconstruction. However, they did not mention characteristics of the recurrent cases nor the duration of follow-up. Rosenbaum *et al*., [352] and Javali *et al*., [353] retrospectively analysed the outcomes of BMG FGU for ReDo urethroplasty in 51 and 21 patients, respectively, using the other cheek as donor side. Patency rates were 82-86%, which is in the range of primary cases.

Vetterlein *et al*., [354] compared primary (no previous open urethroplasty) vs. ReDo (previous open urethroplasty with BMG) vs. secondary (previous open urethroplasty without use of BMG) cases in a retrospective series of 534 patients with BMG FGU. The patency rates in primary and ReDo cases were comparable (87%) whilst the outcome in secondary cases was worse (71%).

A small series (n=37) reported on the use of EPA for revision surgery after failed urethroplasty in strictures of 2.1 (range 1-3.5) cm length on average. Patency rates using EPA after failed primary EPA (51%) and after any other technique of urethroplasty (49%) were 95 and 94% respectively with a mean follow-up of 30 months [321].

Summary of evidence	**LE**
Buccal mucosa free graft urethroplasty after failed urethroplasty achieves the same patency rates as primary cases.	3

Recommendation	**Strength rating**
Use oral mucosa free graft urethroplasty for ReDo urethroplasty in case the of a long stricture.	Strong

*6.3.3 **Urethroplasty for penobulbar or panurethral strictures***

The possibilities for reconstruction are various and often include combinations of different techniques or grafts other than OMG. The patency rates are usually lower than in shorter reconstructions (Table 6.7). Hussein *et al*., [355] performed a RCT comparing skin grafts vs. skin flaps in strictures of mean length 15 cm and found no difference in patency rates (72% vs. 79%) or complications.

Warner *et al*., [305] performed a multi-institutional review in 2015 including 466 patients with stricture length > 8 cm and found an overall patency rate of 77.5%. As discussed previously, Kozinn *et al*., [257] reported on the outcome of staged urethroplasty in a cohort of which 54.9% had panurethral strictures (Table 6.7).

Kulkarni *et al*., [356] proposed a one-stage completely perineal approach with invagination of the penis and one-sided urethral dissection. After 59 months the overall patency rate was 83.7% in 117 men with a mean stricture length of 14 cm.

Another option in patients refusing or unfit for complex reconstructive surgery is PU (see section 6.3.4 Perineal urethrostomy).

Table 6.7: Study characteristics and patency rates of series on penobulbar strictures

Author	Study	Length in cm (min, mean, range)	Technique	N	FU months (mean, range)	Patency
Hussein *et al*. 2011 [355]	RCT	NR, 15, 9-21	Skin graft vs. flap	37	36, 12-60	72 vs. 79%
Hussein *et al*. 2016 [357]	Prospective	NR, 8, NR	BM vs. skin dorsal onlay	69	56, NR	90 vs. 84%
Warner *et al*. 2015 [305]	Retrospective review	> 8, 12.5, 8-24	BM/staged/skin	466	20, 12-344	77.5%
El Dahshoury *et al*. 2009 [358]	Retrospective	NR, 18, 15-20	Skin flap	30	24, NR	87%
Mathur *et al*. 2010 [359]	Retrospective	NR, 12, 8-16.5	Tunica albuginea graft	86	36, NR	89%
Meeks *et al*. 2010 [360]	Retrospective	NR, 11, 4-24	Abdominal skin graft	21	28, 11-52	81%
Kulkarni *et al*. 2012 [356]	Retrospective	NR, 14	BM dorsal onlay	117	59, NR	83.7%
Tabassi *et al*. 2014 [361]	Retrospective	NR, 14.4, NR	BM dorsal onlay	117(37)	19, NR	84%
Xu *et al*. 2017 [301]	Retrospective	> 8, 12, 8-20	BM/LM/combination	81	>12, 41, 15-86	83%
Alsagheer *et al*. 2018 [362]	Retrospective	> 8, 11.3	BM onlay vs. skin flap	50	NR, 16, NR	70 vs. 77%
Kozinn *et al*. 2013 [257]	Retrospective	NR, 9.6, 4-17	Staged urethroplasty	91	15, 12-69	90.1%

BM = buccal mucosa; LM = lingual mucosa; FU = follow-up; N = number of patients; NR = not reported; RCT = randomised controlled trial.

Summary of evidence	LE
Publications about panurethral urethroplasties generally come from high volume centres.	4
Different materials and techniques might be needed for reconstruction.	3

Recommendations	Strength rating
Offer panurethral urethroplasties in specialised centres because different techniques and materials might be needed.	Weak
Combine techniques to treat panurethral strictures if one technique is not able to treat the whole extent of the stricture.	Weak

*6.3.4 **Perineal urethrostomy***

6.3.4.1 Indications

Perineal urethrostomy offers a permanent or temporary solution for restoration of voiding in men with complex urethral stricture disease in whom:

- there are no further options to restore urethral patency either due to multiple previous failed urethroplasties [305, 339] or multiple co-morbidities precluding a more expansive surgical undertaking after failed endoscopic management [363];
- there is a lack of certainty on behalf of the surgeon regarding the most appropriate form of urethroplasty for the patient;
- following urethrectomy and/or penectomy for cancer [364].

6.3.4.2 Types of perineal urethrostomy

Johanson described an inverted anterior scrotal funnel PU in 1953. This was later modified by Gil-Vernet and Blandy to utilise a posteriorly based scrotal flap. Both these techniques utilise an inverted U or lambda incision. The Gil-Vernet-Blandy PU has been further modified with the addition of dorsal and/or ventral free OMG augment

to allow use of PU in men with strictures consequent to radiotherapy [365] or LS [259] and/or in men with PU stenosis or stricture extending into the proximal bulbar or membranous urethra ("augmented Blandy") [363].

More recently, the '7 flap' PU utilising a unilateral posteriorly based scrotal flap has been developed for use in the very obese, or in men of all BMI with stricture extension into the proximal bulbar or membranous urethra [366]. Initially this was performed with transection of the distal bulbar urethra but latterly the technique has been modified to a non-transection technique with loop mobilisation of the bulbar urethra ("loop PU") [367]. The "7-flap" utilises a midline incision – which has been shown to have a significantly reduced side-effect profile in terms of superficial wound infection (1.9% c.f. 18.6%) and superficial wound dehiscence (11.9% c.f. 23.3%) than the inverted U or lambda incision [368, 369] and may be associated with improved urethroplasty (and by inference PU) outcomes, at least in the short term (0% failure c.f. 6.2% failure at six months) [368]. Operative time is similar for all types of PU with mean operative time varying between 97.2 minutes to 112 minutes [364, 370].

The utilisation of PU is increasing [371] – constituting 4.5% of 403 procedures for complex urethral stricture disease in a tertiary centre in 2008 and 38.7% in 2017 [372]. Perineal urethrostomy patients are generally older than those having urethroplasty with a median of 62.6 years of age for men having PU in Fuchs *et al*., 2018 series compared with a median of 53.2 years for men having anterior urethroplasty [372]. Between 18.7% and 73.4% of men having staged urethroplasty for complex anterior urethral stricture decline to proceed to 2nd stage re-tubularisation after a successful 1st stage and remain voiding from the PU of their 1st stage urethroplasty [257, 339, 342].

6.3.4.3 Outcomes

6.3.4.3.1 Patency rates

Patency rates of 70-95% at mean/median follow-up of 20–63 months have been described [305, 339, 347, 363-366, 370, 372]. All reports are retrospective series – all of which are heterogenous in terms of indications and patients. There is consequently little data available to determine which is the best technique for PU.

McKibben *et al*., reported a patency rate of 92.9% in 42 patients for "7-flap" PU at median follow-up of 53.6 months, whilst they had a 100% patency rate with loop PU in twenty patients at a median follow-up of thirteen months [367].

Lumen *et al*., in 2015 reported a 74.3% patency rate for Johanson PU compared with an 87.5% patency rate for Gil-Vernet-Blandy PU (p=0.248), but with a significantly longer follow-up after Johanson PU (median 36 vs. nine months) [364]. Barbagli *et al*., published the largest series of PU patients to date – including 173 men (all of whom had been planned to have a staged urethroplasty for their complex anterior urethral stricture disease and 127 (73.4%) of whom declined to proceed with 2nd stage re-tubularisation). The median follow-up in this series was 62 months and the patency rate was 70% - confirming that patency rates for PU (and indeed for all urethroplasty [273, 346]) reduce with time [339].

See supplementary Table S6.11 for further information.

6.3.4.3.2 Complications

Perineal urethrostomy complications occur in 2.5-11.4% and include superficial wound dehiscence, scrotal abscess, UTI and urosepsis, bleeding, and transient scrotal pain and numbness [305, 364, 373]. The majority of complications are Clavien-Dindo grades 1 (2.9-18.8%) and 2 (0-2.9%). Grade 3 complications are rare and only occur in 5.7-6.2%. In the medium-term 22.2-30.8% of men with PU report post-micturition dribble [364].

6.3.4.3.3 Patient reported outcomes

Barbagli *et al*., reported that 168/173 (97.1%) of men were satisfied or very satisfied with the outcome of their Gil-Vernet-Blandy PU and would have the procedure again at median 62 months follow-up. Of these, 166/173 (95.9%) felt they had excellent or good results from their Gil-Vernet-Blandy PU, 145/173 (85%) felt it caused them no problems and 141/173 (82%) felt it caused their partner no problems [339]. The Trauma and Urologic Reconstructive Network of Surgeons (TURNS) collaborative found no significant change in sexual function and a significant improvement in urinary symptoms following PU in a small group of patients [374], whilst Lumen *et al*., found satisfactory or acceptable International Prostate Symptom Score (IPSS) outcomes in 26/32 (81.25%) of men with Johanson or Gil-Vernet-Blandy PU at a median follow-up of 32 months and nine months, respectively.

McKibben *et al*., found a mean patient global impression of improvement (PGI-I) of 1.3 in nineteen patients with either loop PU or "7-flap" PU [367] at median 31 months follow-up.

6.3.4.3.4 Risk factors for patency failure of the perineal urethrostomy

Lichen sclerosus, trauma and infection urethral strictures have poorer outcomes from PU, with PU patency failure in 36.7-67% at a median 62 month follow-up [339, 373]. Worse outcomes were also observed in patients with previous failed urethroplasty and multiple previous endoscopic and open treatments [339, 364, 365].

Barbagli *et al*., found that stricture length was inversely related to PU patency, as was patient age [339]. Conversely Viers *et al*., found outcomes worsened with age, reporting patency rates of 100% in men < 50 years old compared with 83% in men aged 60-69 years old [347]. Lopez *et al*., found increased risk of PU failure in men with ischaemic heart disease which makes sense and would be a putative explanation for the age-related worsening of outcomes noted by Viers *et al*., [373].

Failure of PU is most commonly treated with surgical revision of PU using V-Y plasty, augmentation or complete ReDo but can also be managed with periodic dilatation or urinary diversion [339, 363, 364].

For further information see supplementary Table S6.11.

Summary of evidence	LE
Perineal urethrostomy provides very good short- and long-term outcomes for men with complex urethral stricture disease.	1a
Perineal urethrostomy (PU) provides very good short and long-term outcomes for men who are unable to have complex reconstruction due to co-morbidities.	2b
All types of PU yield equivalent very good outcomes.	4
Augmented Gil-Vernet-Blandy or "7-flap" PU yield very good outcomes in men with extension of their urethral stricture disease into the proximal bulbar or membranous urethra.	2
"7-flap" PU yields very good results in obese men.	3

Recommendations	Strength rating
Offer perineal urethrostomy (PU) as a management option to men with complex anterior urethral stricture disease.	Strong
Offer PU for men with anterior urethral stricture disease who are not fit or not willing to undergo formal reconstruction.	Weak
Choose type of PU based on personal experience and patient characteristics.	Weak
Consider augmented Gil-Vernet-Blandy perineal urethrostomy or "7-flap" PU in men with proximal bulbar or membranous urethral stricture disease.	Weak
Consider "7-flap" urethroplasty in obese men.	Weak

*6.3.5 **Posterior urethra***

6.3.5.1 Non-traumatic posterior urethral stenosis

6.3.5.1.1 Treatment of non-traumatic posterior urethral stenosis

Several treatment modalities including conservative management (see section 6.1 Conservative options), endoluminal, open or minimally invasive surgical procedures are currently available, depending on patient's goals and health status.

6.3.5.1.2 Endoluminal management of non-traumatic posterior urethral stenosis

6.3.5.1.2.1 Dilatation of non-traumatic posterior urethral stenosis

This can be done under loco-regional anaesthesia [375-379]. Dilatation is used for VUAS [375-380] or radiation induced BMS [381] and in the majority of reported cases, patients were not previously treated for their stricture (see supplementary Table S6.12). Patency rates vary widely between 0-89% [117, 375-381]. The risk of *de novo* UI was low (0-11%) and no other complications were reported. It is of note that most series report on visually controlled dilatation [375-379] in VUAS without complete obliteration.

6.3.5.1.2.2 Endoscopic incision/resection of non-traumatic posterior urethral stenosis (Table 6.8)

Incisions can be performed at multiple locations according to surgeon's preference [382]. However, aggressive incisions at the six and twelve o'clock positions should be avoided because of the risk of, respectively, rectal injury and urosymphyseal fistulation [189, 383-385]. The risk of urosymphyseal fistulation is especially a concern after previous radiotherapy [386]. Result of bladder neck incision for VUAS are poorer after radiotherapy [387].

Direct vision internal urethrotomy is mainly performed in patients with primary or recalcitrant VUAS although one series performed it in a mix of patients with VUAS and BNS [388] and two series reported it for radiation-induced BMS [117, 381]. Direct vision internal urethrotomy/ dilatation for non-irradiated BMS are usually included in series reporting on anterior strictures (see section 6.2 Male endoluminal treatment of anterior urethral strictures). Patency after a 1st "cold/hot knife" DVIU ranges between 25-80% [375, 376, 380, 382, 388-393]. Laser incision yields a 69-100% patency rate [376, 380, 394, 395]. In a retrospective and unbalanced series, La Bossiere *et al*., found better patency rates for laser incision as compared to dilatation, "cold knife" DVIU and transurethral resection (TUR) [376]. Redshaw *et al*., reported inferior patency rates for "cold knife" incision vs. "hot knife" incision followed by MMC for BNS (50 vs. 63%; p=0.03) [236] (see supplementary Table S6.13).

Urinary incontinence largely varies between 0 and 53% but some series have not assessed urinary continence before DVIU [389, 391]. In series where pre- DVIU continence data were available, *de novo* urinary continence after DVIU ranges between 0% and 10% [375, 380, 390, 392, 394]. Noteworthy, of 21 patients that were incontinent pre-DVIU in the series of Giannarini *et al*., eleven (52%) patients became continent, and eight (38%) patients experienced improvement after DVIU [390]. As most recurrences will occur early [390, 391], it is advised to wait for three to four months after DVIU [382, 391, 396] to proceed with incontinence surgery, if necessary, although others wait for twelve months [397]. The presence of recurrence must be ruled out by cystoscopy prior to incontinence surgery [382, 391, 396, 397].

Another option is to resect the stenosis. Popken *et al*., reported a 47% patency rate with TUR for untreated VUAS and no patient suffered *de novo* SUI [392]. Kranz *et al*., compared the results of TUR in 87 and 60 patients with, respectively, VUAS after RP and BNS after TURP. After a median follow-up of 27 (range: 1-98) months, patency rate was 40.2% for VUAS and 58.3% for BNS (p=0.031). The rate of *de novo* incontinence was significantly higher in patients treated for VUAS compared to BNS (13.8 vs. 1.7%; p=0.011) [398]. There is conflicting evidence whether resection is associated with higher incontinence rate compared to incision. [379, 399] Brodak *et al*., compared TUR by bipolar resection (n=22) with holmium laser incision and vaporisation (n=17). After a mean follow-up of 42 months, two (9.1%) and four (23.5%) patients suffered a recurrence with bipolar and laser resection respectively (p=0.37). After six months, patients treated with bipolar resection had a significant better Qmax compared to laser treatment (13 vs. 6.1 ml/s; p < 0.001) [395]. Bipolar plasma vaporisation produced an 82% patency rate at a mean 24-month follow-up in 28 patients with VUAS who previously failed endoscopic treatment [400].

Cut-to-the-light technique for a complete obliterative stricture is not advised because of the very-low likelihood of durable patency and for the risk of false passage towards the rectum [396, 401, 402].

Repeat DVIU was often able to stabilise the stricture [117, 375, 376, 381, 388-390, 398], but ultimately 6-10% required urinary diversion [391] or chronic suprapubic cystostomy [381, 388].

Transurethral resection can be performed for prostatic obstruction due to sloughing after high-energy treatments (HIFU, cryoablation) [100]. Transurethral resection for obstructive necrotic debris after radiotherapy is possible but is of limited role. Risk of recurrence is 50% and risk of *de novo* UI is 15-25% [100].

Table 6.8: Results of endoluminal incision/resection for posterior non-traumatic stenosis

Study	Modality	Type	N	Previous treatment (%)	FU (months)	Patency° (%)	Urinary incontinence (%)	Complications (%)
Merrick *et al*. [381]	Dilatation/ "Cold knife" DVIU	Radiation-induced BMS	29	0	NR	69	NR	NR
Sullivan *et al*. [117]	Dilatation (n=15) / "Cold knife" DVIU (n=20)	Radiation-induced BMS	39	0	16 (2-48)	51	11	NR
Brede *et al*. [391]	"Cold knife" DVIU	VUAS	63	Dilation 33 Incision 38 Both 29	11 (1-144)	73	52*	NR
Yurkanin *et al*. [389]	"Cold knife" DVIU	VUAS	61	Dilatation 100	31 (1-77)	87	12**	NR

Giannarini *et al*. [390]	"Cold knife" DVIU	VUAS	43	0	48 (23-80)	74	0	NR
Ramchandani *et al*. [375]	"Cold knife" DVIU	VUAS	10	0	NR	80	10	0
Hayashi *et al*. [380]	"Cold knife" DVIU	VUAS	6	Dilatation: 100	NR	50	NR	NR
	Holmium laser DVIU	VUAS	3	Dilatation + DVIU: 100	11-37	100	0	NR
Lagerveld *et al*. [394]	Holmium laser DVIU	VUAS	10	None: 40 Endoscopic (dilatation +/- DVIU +/- ISD): 60	18 (3-29)	100	0	0
Ramirez *et al*. [388]	"Hot knife" DVIU	VUAS: 74% BNS: 26%	50	None: 22	16	72	9	NR
Gousse *et al*. [393]	"Hot knife" DVIU	VUAS	15	None	15 (6-26)	80	100***	NR
Bang *et al*. [382]	"Hot knife" DVIU	VUAS	37	NR	13 (2-33)	65	100***	NR
Popken *et al*. [392]	"Cold knife" DVIU	VUAS	6	None	12-72	50	0	NR
	TUR	VUAS	15	None		47	0	NR
Kranz *et al*. [398]	TUR	VUAS	87	NR	27 (1-98)	40.2	13.8	NR
	TUR	VUAS	60	NR		58.3	1.7	NR
Brodak *et al*. [395]	TUR (bipolar)	BNS	22	DVIU 45	42 (14-72)	91	NR	NR
	Holmium laser DVIU	VUAS	17	DVIU: 12		76	NR	NR
Ozturk *et al*. [400]	TUR (bipolar)	VUAS	28	Dilatation: 75 DVIU: 25	24 (6-66)	82	0	0
LaBossiere *et al*. [376]	Holmium laser DVIU	VUAS	70	NR	10	69	NR	NR
	"Cold knife" DVIU	VUAS	8	NR		25	NR	NR
	TUR	VUAS	36	NR		39	NR	NR

BNS = bladder neck stenosis; DVIU = direct vision internal urethrotomy; FU = follow-up;
ISD = intermittent self-dilatation; NR = not reported; TUR = transurethral resection;
VUAS = vesico-urethral anastomosis stricture.
°patency rate after 1st endoluminal treatment evaluated in the study.
** requiring incontinence surgery (artificial urinary sphincter or male sling).*
*** slightly problematic urinary incontinence by questionnaire post DVIU (no data on pre DVIU continence).*
****all incontinent pre-operatively.*

6.3.5.1.2.3 Post-dilatation/direct vision internal urethrotomy strategies for non-traumatic posterior urethral Stenosis

6.3.5.1.2.3.1 Intermittent self-dilatation for non-traumatic posterior urethral stenosis

As for anterior strictures, ISD can be offered to patients for recurrent posterior stenosis after dilation/DVIU to stabilise the stenosis. This is especially relevant for patients unfit/unwilling to undergo surgery or in patients with radiation-induced BMS [117, 376, 381, 403]. Although ISD may be acceptable to many urologists and patients, it usually is associated with a reduced QoL and poor patient compliance [33].

6.3.5.1.2.3.2 Intralesional injections for non-traumatic posterior urethral stenosis

In order to stabilise the luminal fibrosis and consequently to reduce the risk of recurrence, injection of antifibrotic agents at the time of endoluminal treatment has been proposed. The majority of patients in these studies were patients with recalcitrant/recurrent non-obliterative VUAS/BNS. Two series used corticosteroids [379, 396], whilst the others used MMC [397, 401-405]. Patency rates with corticosteroid injections range between 50-100% [379, 396]. Patency rates with MMC vary between 50-94% [397, 404-406]. No trials comparing endoluminal treatment with or without adjuvant intralesional injections were identified.

See supplementary Table S6.13 for further information.

Complications are low across most studies, but all studies were retrospective in nature. Redshaw *et al*., also reported grade 3 complications in four out of 55 (7%) patients, including osteitis pubis (n=2), bladder neck necrosis (n=1) and rectourethral fistula (n=1) in one multi-institutional study [404]. Three of these patients ultimately required urinary diversion with additional faecal diversion in one patient [404]. Given the severity of these complications, although rare, MMC should not be used outside the framework of a clinical trial [407].

6.3.5.1.2.3.3 Urethral stent for non-traumatic posterior urethral stenosis

Stents have been used anecdotally in the posterior urethra [247, 248, 376]. Patency rates are relatively low (47-60%) [247, 248, 376] at the cost of a high-risk for UI (19-82%) [247, 248].

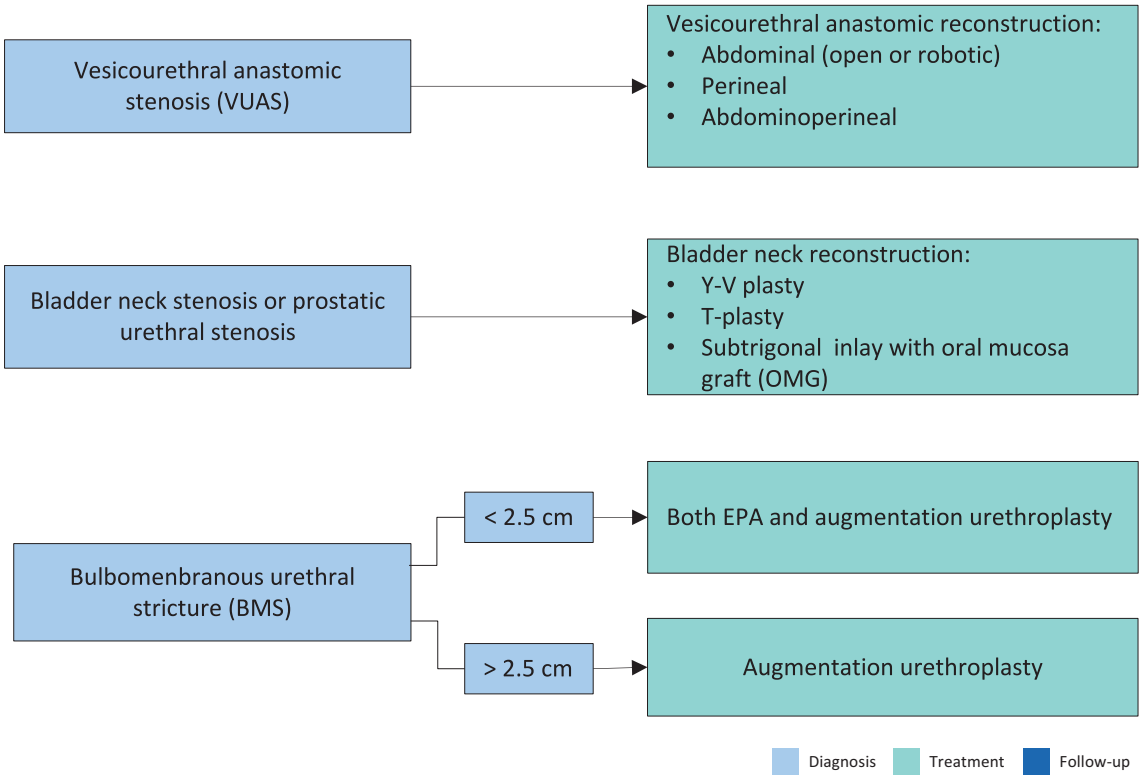
Summary of evidence	**LE**
For non-obliterative VUAS and radiation-induced BMS, visually controlled dilatation and DVIU yield a patency rate of respectively 0-89% and 25-100% with a low complication rate. It can be performed under loco-regional anaesthesia.	3
During DVIU, deep incision might provoke injury to the rectum at the six o' clock position and might provoke uro-symphyseal fistulation at the twelve o'clock position.	3
For BNS, TUR and "hot-knife" incision yield a patency rate of respectively 58.3 and 72% with a low complication rate.	3
Repeat endoluminal treatments in non-obliterative VUAS, radiation-induced BMS or BNS can stabilise the posterior stenosis and are easy to perform compared to reconstructive surgery.	3
Any form of endoluminal treatment might be associated with *de novo* UI (up to 25%) or worsening of existing UI (up to 15%).	3
Vesico-urethral anastomosis stricture, BMS and BNS with complete obliteration are not included in present series and endoluminal treatment is unlikely to be successful.	3
Urethral stents at the posterior urethra have a rather low patency rate (47-60%) and incontinence rate (19-82%).	3

Recommendations	**Strength rating**
Perform visually controlled dilatation or direct vision internal urethrotomy (DVIU) as 1st line-treatment for a non-obliterative vesico-urethral anastomosis stricture (VUAS) or radiation-induced bulbomembranous strictures (BMS).	Weak
Do not perform deep incisions at the six and twelve o' clock position during DVIU for VUAS or radiation-induced BMS.	Strong
Perform transurethral resection (TUR) or "hot-knife" DVIU as 1st line-treatment for patients with non-obliterative bladder neck stenosis (BNS) after surgery for benign prostatic obstruction.	Strong
Perform repeat endoluminal treatments in non-obliterative VUAS or BNS in an attempt to stabilise the stricture.	Weak
Warn patients about the risk of *de novo* urinary incontinence (UI) or exacerbation of existing UI after endoluminal treatment.	Weak
Do not perform endoluminal treatment in case of VUAS, BMS and BNS with complete obliteration.	Strong
Do not use stents for strictures at the posterior urethra.	Weak

6.3.5.1.3 Lower urinary tract reconstruction for non-traumatic posterior urethral stenosis

If endoluminal treatment (repeatedly) fails or in case of a completely obliterated posterior stenosis [401, 402, 408, 409], lower urinary tract (LUT) reconstruction may be considered in fit patients motivated to undergo surgery (Figure 6.1). The choice of LUT reconstruction will depend upon the length, location, calibre and aetiology of the stenosis, continence status, bladder function, previous radiotherapy, patient's preference, and surgeon's expertise.

Figure 6.1: Options for lower urinary tract reconstruction of non-traumatic posterior urethral obstruction (stenosis/stricture)



6.3.5.1.3.1 Redo vesico-urethral anastomosis for vesico-urethral anastomotic stenosis after radical prostatectomy

After excision of the stenosis, ReDo vesico-urethral anastomosis (ReDo VUA) can be performed. This may be performed via a retropubic, perineal, combined abdominoperineal or robot-assisted approach. Nikolavsky *et al*., proposes a retropubic approach for VUAS involving the bladder neck, a perineal approach for short VUAS with intact bladder neck and an abdominoperineal approach for long segment (> 3 cm) VUAS with bladder neck involvement [408]. The ReDo VUA must be performed in a tension-free fashion which can be achieved either by mobilisation of the bladder (retropubic approach), mobilisation of the bulbar urethra with corporal splitting and inferior pubectomy if necessary (perineal approach) or both (abdominoperineal approach) [408, 410]. Dinerman *et al*., reported a robot-assisted abdominoperineal approach in a case with 4.5 cm long complete obliteration [411]. Kirshenbaum *et al*., reported a pure robot-assisted abdominal approach. Regardless of the approach, the procedure is technically demanding due to the location deep under the pubic symphysis, and the proximity of the external sphincter [410]. As a consequence, surgical morbidity must be considered. As most patients with VUAS were healthy enough to undergo RP, most patients will likewise remain fit and eligible for VUAS surgical reconstruction [408, 410].

Table 6.9: Outcomes of redo vesico-urethral anastomosis

Study	N	Approach (%)	Previous RT (%)	FU (months)	Length (cm)	Patency (%)	Incontinence (%)	Complications (%)
Nikolavsky *et al*. [408]	12	Perineal: 25 Abdominal: 67 Abdominoperineal: 17	25	76 (14-120)	2.5 (1-5)	67	58	Persistent extravasation due to anastomotic dehiscence grade 3b: 8.3 (prior RT)
Mundy *et al*. [410]	17	Transperineal	0	NR	NR	88	100	NR
	6		100	NR	NR	67	100	NR
Schuettfort *et al*. [412]	22	Transperineal	0	45 (4-77)	NR	91	100*	Rectal injury: 4 Lower leg paresthesia: 4
	1		100		NR	0	100*	

Pfalzgraf *et al*. [413]	20	Retropubic	NR	63 (15-109)	NR	60	65**	UTI: 5 Fever: 5 Renal failure: 5 (all grade 2)
Giudice *et al*. [414]	10	Perineal: 5 Abdominal: 4 Combined: 1	NR	30 (4-106)	NR	80	70	NR
Dinerman *et al*. [411]	1	Robot-assisted abdominoperineal	0	12	4.5	100	0***	0
Kirshenbaum *et al*. [409]	5	Robot-assisted abdominal (±VY-plasty)	0	14 (5-30-)	NR	60	0	Pubovesical fistula: 20 grade 3b

FU = follow-up; NR = not reported; RT = radiotherapy; UTI = Urinary tract infection.
** incontinent before ReDo VUA.*
*** de novo incontinence in four out of eleven patients.*
****social continent (1 pad/day).*

ReDo VUA in non-irradiated patients yields patency rates of 60-91% (Table 6.9) [408-410, 412-414]. Prior radiotherapy is a risk factor for failure [410, 412]. In addition, radiation-induced bladder toxicity might provoke reduced bladder capacity, low bladder compliance, bladder spasms and pain, and urethral necrosis making reconstruction futile (see below) [386, 410, 415]. ReDo VUA should only be done in patients with adequate bladder function and in the absence of (peri)-urethral pathology (urethral necrosis, calcification, fistulation). Flaps (gracilis flap, peritoneal flap) to support and protect the anastomosis may be beneficial in irradiated patients [408].

With the transperineal approach, UI is inevitable, as this approach disrupts the external sphincter [409, 410, 412, 414]. With the retropubic approach, Pfalzgraf *et al*., reported *de novo* incontinence in only four out of eleven (36%) patients [413]. In the series of Nikolavsky *et al*., where a retropubic approach was predominantly used, incontinence rate was 58% [408]. Kirshenbaum *et al*., reported no incontinence in five patients treated by robot-assisted retropubic approach [409]. Giudice *et al*., reported incontinence in one out of four patients treated with the retropubic approach [414]. Therefore, some authors [100, 408, 409] have proposed a preference for the retropubic approach in patients with good pre-operative urinary continence, although both approaches have never been directly compared for UI. In addition, the lack of perineal dissection by a retropubic approach will preserve the perineal anatomy and vascularisation which makes subsequent artificial urinary sphincter (AUS) less demanding [409]. Artificial urinary sphincter implantation should be deferred because of the risk of VUAS recurrence and difficulty of treating any recurrent VUAS with the cuff of the AUS in place [391, 410]. The exact timing of AUS placement is not consensual in the literature but most advise waiting at least three to six months to ensure stability of the VUA patency [386, 407, 410, 412].

Due to the complexity of this pathology the EAU Urethral Strictures Panel advises that VUAS reconstruction should be performed only in experienced high-volume centres, particularly after prior radiotherapy or other energy ablative treatments.

Summary of evidence	**LE**
ReDo VUA has patency rates of 60-91% in non-irradiated patients and 67% in irradiated patients with obliterative VUAS or VUAS refractory to endoluminal treatment.	3
Urinary incontinence is inevitable after transperineal ReDo VUA. Artificial urinary sphincter placement can be offered after three to six months if patency of ReDo VUA is ensured.	3
De novo incontinence with retropubic ReDo VUA is 0-58%.	3

Recommendations	Strength rating
Perform ReDo vesico-urethral anastomosis (VUA) in non-irradiated patients and irradiated patients with adequate bladder function with obliterative vesico-urethral anastomosis stricture or vesico-urethral anastomosis stricture refractory to endoluminal treatment.	Weak
Warn patient that urinary incontinence (UI) is inevitable after transperineal ReDo VUA and that subsequent anti-UI surgery might be needed in a next stage, after at least three to six months.	Strong
Offer ReDo VUA by retropubic approach if the patient is pre-operatively continent.	Weak

6.3.5.1.3.2 Posterior stenosis after surgery for benign prostatic obstruction

6.3.5.1.3.2.1 Bladder neck reconstruction for bladder neck stenosis after surgery for benign prostatic obstruction

The bladder neck is augmented by advancement of local bladder flaps (Y-V or T-plasty) with or without resection of scar tissue. They are used for BNS refractory to endoscopic treatments [409, 416-418]. Patency rates vary between 83-100% with fourteen to 45 months follow-up [409, 416-418]. There is a trend to perform bladder neck reconstruction by minimally invasive approach (laparoscopic, robot-assisted) [409, 417, 418]. *De novo* incontinence rate ranges from 0-14% [409, 416-418]. Satisfaction among patient is high with 88.5% of patients stating that they are pleased with the surgery, with an improvement of QoL in 75% of patients [416, 418]. Recently, a robot-assisted augmentation technique with subtrigonal buccal mucosa inlay has been successfully reported in a case report, but this technique requires further investigation [419].

See supplementary Table S6.14 for further information.

6.3.5.1.3.2.2 Bulbomembranous strictures after surgery for benign prostatic obstruction

Bulbomembranous urethral strictures (BMS) after TURP or simple prostatectomy are managed as bulbar strictures and can be treated by EPA or augmentation urethroplasty with a graft, taking into account the length and tightness of the stricture [82]. Kulkarni *et al*. reported a similar patency rate for dorsal and ventral onlay urethroplasty (resp. 81.8% versus 84.6% after mean follow-up of 14 months) [420]. As reconstruction is in the proximity of the external sphincter and the bladder neck was already damaged during BPO surgery, the risk of incontinence (up to 25%) is present [82].

Summary of evidence	LE
Bladder neck reconstruction with Y-V or T-plasty for treatment refractory BNS has patency rates of 83-100%.	3
Incontinence occurs in up to 14% with bladder neck reconstruction and up to 25% after reconstruction of BMS after previous surgery for BPO.	3

Recommendations	Strength rating
Perform bladder neck reconstruction with Y-V or T-plasty for treatment refractory bladder neck stenosis (BNS).	Weak
Warn patients about *de novo* urinary incontinence after reconstruction for BNS or bulbomembranous urethral strictures with previous benign prostatic obstruction surgery as aetiology.	Strong

6.3.5.1.3.3 Radiation/high-energy induced posterior strictures

6.3.5.1.3.3.1 Bulbomembranous strictures secondary to radiation/high energy sources

The major challenge in treating radiation-induced strictures is the consequent tissue damage with impaired healing capacity, involving not only the stricture itself but also the adjacent proximal and distal areas of the scar [421]. Additionally, proximity of the stricture to the external sphincter can further complicate surgery [421]. Due to these challenges, patients with radiation-induced BMS have long been considered poor candidates for urethral reconstruction and have been treated with urinary diversion if endoscopic treatments failed or were not possible [421].

Most radiation-induced BMS are short and in these cases, EPA is possible avoiding the use of a graft or a local flap in an area of poor vascular health. However, EPA will not be possible for BMS with a long bulbar segment and in these cases, augmentation urethroplasty will be necessary despite the aforementioned concerns. A

systematic review reported a pooled patency rate of 80% with no significant differences between type of urethroplasty (EPA versus augmentation urethroplasty). Stress UI was reported in 19% of cases [421]. Rourke *et al*., reported no significant differences between EPA and augmentation urethroplasty regarding *de novo* UI (26 vs. 25%; p=1), new onset ED (35 vs. 0%; p=0.06) or other adverse events (30% vs. 33%; p=1) [422].

6.3.5.1.3.3.2 Prostatic strictures secondary to radiation/high energy sources

Radiotherapy and high-energy modalities (cryoablation, HIFU) might provoke prostatic necrosis, sloughing and obstruction [100]. Cases refractory to TUR and with good bladder capacity might be salvaged by prostatectomy taking into account the morbidity associated with salvage RP (rectal injury, VUAS, incontinence) [100, 423]. Mundy *et al*., treated nine patients with patency in six, (67%) and one (11%) needing an AUS for severe incontinence [410].

Cases with impaired bladder function, urethral necrosis and/or peri-urethral pathology should be considered for supravesical diversion, especially if a suprapubic catheter is not tolerated due to bladder pain or spasms [386, 407, 410, 415].

Recently, a "pull-through" procedure has been reported as an alternative to cutaneous diversion for reconstruction of the devastated posterior urethra associated with a defunctionalised bladder after radiation where tissue vascularity and quality is poor [424]. This novel technique of total LUT reconstruction combines salvage cystectomy, ileal neobladder formation and urethral pull-through. An AUS was implanted in a second stage. All eight patients maintained a patent posterior urethra after a median follow-up of 58 (range 16-84) months. Five patients experienced low-grade complications after the first stage, but no high-grade complications were reported. Four out of eight (50%) patients experienced cuff erosion with need for removal and subsequent reimplantation. After a median of two revision surgeries (range 0 to 4), all patients achieved social continence enhancing QoL [424]. This technique requires further validation before its use can be recommended.

Summary of evidence	**LE**
Patency rates of urethroplasty for radiation-induced BMS is 80% with no significant differences between EPA and augmentation urethroplasty.	3
Radiation-induced BMS longer than 2-2.5 cm are rarely amenable for EPA.	3
De novo incontinence and new onset ED after urethral surgery for radiation-induced BMS are reported in respectively 19-26% and 0-35% of cases.	3
Salvage prostatectomy can achieve patency in 67% of patients for prostatic strictures after irradiation or high-energy treatments but morbidity is substantial.	4

Recommendations	**Strength rating**
Use either excision and primary anastomosis (EPA) or augmentation urethroplasty for short (< 2.5 cm) radiation-induced bulbomembranous strictures (BMS) refractory to endoscopic treatment depending on surgeon's experience.	Weak
Perform augmentation urethroplasty for long (> 2.5 cm) radiation-induced BMS.	Weak
Warn patients about the risk of *de novo* incontinence and new onset erectile dysfunction after urethroplasty for radiation-induced BMS.	Strong
Offer salvage prostatectomy in motivated and fit patients with adequate bladder function in case of a prostatic stricture due to irradiation or high-energy treatment.	Weak

6.3.5.1.4 Extirpative surgery and urinary diversion for non-traumatic posterior urethral stenosis

In complex and/or recurrent cases [408], LUT reconstruction is not possible or not indicated due to severe necrosis, calcification and significant morbidity, especially severe pain [407]. Intractable haematuria or fistulation might be other reasons to abandon the urethral outlet. Typically, the patient has a history of pelvic irradiation or high energy prostate cancer treatment and several previous attempts to achieve cure. Moreover, and equally important, any of the options used to deal with a devastated posterior urethra are dependent upon good bladder capacity, compliance and function allowing for bladder preservation as well as healthy distal ureters [386, 407]. The last resort therapeutic option is urinary diversion (continent or incontinent) with or without cystectomy [410, 415]. Different techniques have been described and the choice between them largely

depends on the bladder capacity, presence of local symptoms, performance status and expectations of the patient. Cystectomy during urinary diversion is able to palliate symptoms of intractable bladder pain, spasms and haematuria which are especially prevalent after pelvic radiotherapy [425-428]. The satisfaction rate was reported to be 100% and the overwhelming majority of patients would have undergone this extirpative surgery an average of thirteen months sooner in a study of fifteen patients by Sack *et al*., [429]. In a report by Faris *et al*., 27% of the patients also required bowel diversion due to intractable gastrointestinal morbidity, highlighting the complexity of this pathology [415].

Summary of evidence	**LE**
Urinary diversion can improve QoL in patients with a devastated lower urinary tract with a high satisfaction rate.	3
Cystectomy is able to palliate symptoms of intractable bladder pain, spasms, and haematuria.	3

Recommendations	**Strength rating**
Perform urinary diversion in recurrent or complex cases with loss of bladder capacity and/or incapacitating local symptoms.	Weak
Perform cystectomy during urinary diversion in case of intractable bladder pain, spasms and/or haematuria.	Weak

6.3.5.2 Post-traumatic posterior stenosis

The acute and early management of PFUIs is discussed in the EAU Guidelines on Urological Trauma. A nonobliterative stenosis is the result of a partial injury at the membranous urethra or occurs after unsuccessful early realignment of a partial or complete injury. An obliterative stenosis is the consequence of a complete injury with a distraction defect between the ruptured urethral ends. The gap between these ends fills up with dense fibrotic tissue [11].

The deferred management of PFUI is at earliest three months after the trauma. After that period, the pelvic haematoma has nearly always resolved, the prostate has descended into a more normal position, the scar tissue has stabilised [430] and the patient is clinically stable and able to lie down in the lithotomy position [430].

6.3.5.2.1 Endoluminal treatment for post-traumatic posterior stenosis

6.3.5.2.1.1 Endoluminal treatment as primary treatment for post-traumatic posterior stenosis

Endoluminal treatment (dilation, DVIU) of an obliterative stenosis using the cut-to-the light principle will not be successful [46] and has a risk of creating a false passage towards the bladder base or rectum [431]. For a non-obliterative, short (< 1.5 cm) stenosis, one attempt of endoluminal treatment (endoscopic incision or dilation) can be performed. Kulkarni *et al*., reported a 92.3% and 96.5% stricture-free rate with "cold knife" and holmium laser urethrotomy, respectively (median follow-up respectively 61 and 57 months) [432]. These results are challenged by Barbagli *et al*., who reported a 51% stricture-free rate with holmium laser urethrotomy but with no data on length of follow-up available [433]. Cai *et al*., compared patient outcomes between bipolar plasma vaporisation and "cold knife" DVIU in 53 patients with posterior traumatic (80%) and iatrogenic (20%) urethral strictures with significantly different stricture-free rates of 81.5% vs. 53.8% at a mean follow-up of 13.9 months, respectively [434]. No severe complications were reported in either group. A statistically significant shorter operative time was found in the bipolar group [434]. Barratt *et al*,. calculated a composite stricturefree rate of 20% after all types of endoscopic treatments (but with a mix of obliterative and non-obliterative stenoses) [46]. *De novo* UI was reported in 4% of cases [46]. Repetitive endoluminal treatments are unlikely to be curative and must be discouraged as this delays the time to definitive cure and can lead to more complications [435, 436].

6.3.5.2.1.2 Endoluminal treatment after failed urethroplasty for post-traumatic posterior stenosis

In case of a non-obliterative and short (< 1 cm) recurrence after failed urethroplasty, endoluminal treatment can be performed [437]. Although a 1st and 2nd DVIU can be successful with a stricture-free rate of 22.9-77.3% and 0-60% respectively, three or more incisions are never successful (see supplementary Table S6.16) [437-440]. Therefore, repetitive endoluminal treatments (dilations and/or endoscopic incisions) can only be considered as a palliative option [441].

Summary of evidence	LE
Endoluminal treatment of obliterative stenoses is not successful and may create false passages towards bladder or rectum.	3
A 1st DVIU has stricture-free rates of 22.9-77.3% for a short and non-obliterative recurrence after excision and primary anastomosis.	3
Three or more endoscopic incisions are never successful for recurrence after excision and primary anastomosis.	3

Recommendations	Strength rating
Do not perform endoscopic treatment for an obliterative stenosis.	Strong
Perform one attempt at endoluminal treatment for a short, non-obliterative stenosis.	Weak
Do not perform more than two direct vision internal urethrotomies and/or dilatations for a short and non-obliterative recurrence after excision and primary anastomosis for a traumatic posterior stenosis if long-term urethral patency is the desired intent.	Weak

6.3.5.2.2 Urethroplasty for post-traumatic posterior stenosis

In view of the complexity and difficulty of urethroplasty and the fact that the best results are obtained with its first attempt, this surgery must be performed in high-volume centres [442]. It has been calculated that to achieve and maintain sufficient experience in the reconstruction of PFUI, one centre per twelve million inhabitants is sufficient (for well-resourced countries) [443].

6.3.5.2.2.1 First urethroplasty for post-traumatic posterior stenosis

6.3.5.2.2.1.1 Indication and technique of urethroplasty for post-traumatic posterior stenosis

Progressive perineal EPA is the standard treatment for an obliterative stenosis and for a non-obliterative stenosis as first attempt, or after failure of primary endoluminal treatment [46, 444].

Although both a midline and inverted U-incision are possible to gain access to the posterior urethra, a midline incision is associated with a significant reduction in trauma to the superficial perineal and posterior scrotal nerves and vessels, in the rate of surgical site infections (3.1% vs. 16.4%) and reduced length of hospitalisation [369].

A combined transpubic abdomino-perineal approach is only necessary in complicated cases such as those with associated para-urethral bladder base fistula, trauma-related recto-urethral fistula, and bladder neck injury [431]. Total pubectomy during transpubic abdomino-perineal reconstruction has a higher complication rate (bleeding, pelvic instability, dead space) compared to partial (superior or inferior) pubectomy with no gain in surgical exposure [445]. Although also considered complex situations, iatrogenic recto-urethral fistula (after misdirected endoscopic treatment), traumatic recto-urethral fistula < 5 cm from the anus, UCF and urinoma cavity can usually be corrected by a progressive perineal approach only [431, 446].

6.3.5.2.2.1.2 Patency rate after urethroplasty for post-traumatic posterior stenosis

The overall patency rate after deferred EPA is 85.7% [46]. Complete excision of scar tissue is a strong predictor for freedom of stricture whereas number (3-5 vs. 6-7) and size (3.0 vs. 4.0) of sutures are not [447]. A retrospective study showed an improved patency rate after eversion of the urethral mucosa of both urethral ends before anastomosis ("valgus urethral mucosa anastomosis") [448], but this finding has yet to be confirmed in a prospective fashion.

To preserve the antegrade arterial inflow of the bulbar urethra and reduce the surgical trauma of "classic" deferred EPA, bulbar artery sparing EPA has been described [449]. Initial patency rates vary between 88.5-100% with 20-45 months of follow-up (see supplementary Table S6.17) [449-451]. Xie *et al*., only used this technique for distraction defects less than 2.5 cm [451]. No evidence exists to date whether bulbar artery sparing EPA is superior to the "classic" EPA in terms of patency rate and potency and continence rates.

In case of a very deep location of the proximal urethral end that makes anastomotic suturing impossible, Badenoch described a pull-through technique which has a 33.3-96.5% patency rate after 43-126 months of follow-up (see supplementary Table S6.18 for further information) [432, 452, 453]. With the aim to reduce stricture recurrence, Wong *et al*., advise a 1.5 cm segment overlap of the bulbar stump within the prostatic

urethra during the pull-through technique [452]. To facilitate the suturing at the proximal part of the urethra located deep under the pubic bone, the robotic approach is under exploration but there is no evidence so far of improved outcome with this approach [454].

6.3.5.2.2.1.3 Sexual function, urinary continence, and rectal injury after urethroplasty for post-traumatic posterior stenosis

Regarding erectile function, a prospective study by Hosseini *et al*., found no significant difference before, and three or six months after EPA for posterior traumatic stenosis [455]. Another prospective study by Tang *et al*., also demonstrated no significant overall change in ED after urethroplasty. However, in the subgroup of patients with pre-operative non-vascular ED, a significant post-operative increase in ED was observed [456]. A meta-analysis of retrospective studies showed a significant decline of the rate of ED from 43.27% before to 24.01% after posterior urethroplasty ($p < 0.001$) [457]. Assessment of erectile function and its definitive treatment (e.g., penile prosthesis) should be performed two years after the trauma because of the potential return of normal erectile function within that time [458, 459].

After deferred EPA, antegrade ejaculation is present in 98.3-100% of cases [460, 461]. Decreased ejaculatory volume and/or diminished ejaculatory force were reported in 17.2-18.7% of cases but it cannot be assessed whether this is due to the trauma or due to the surgery [460, 461].

Continence after PFUI and urethroplasty is generally attributed to a competent bladder neck [46]. On the other hand, as most ruptures occur at the bulbomembranous junction just below the external sphincteric mechanism, at least a part of the external sphincter mechanism can be spared during urethroplasty [462]. Therefore, incontinence is rare with deferred EPA (6.8-8.5%) and is usually due to incompetence of the bladder neck although an incompetent bladder neck will not necessarily result in incontinence after urethroplasty [46, 462, 463].

Rectal injury is a relatively rare (0-10.2%) but severe complication after deferred EPA (see supplementary Table S6.19) [430, 438, 445, 463-467]. The risk of rectal injury tends to be higher in complicated cases or cases with previous urethral manipulations [430, 468, 469].

6.3.5.2.2.2 ReDo-urethroplasty for post-traumatic posterior stenosis

In case of a recurrent stenosis, a repeat ("ReDo") urethroplasty is possible. In the majority of cases, especially if not all consecutive length-gaining manoeuvres have been used during the 1st EPA, another EPA can be performed [463, 467, 468, 470-472]. The Badenoch pull-through technique is again an option if no adequate mucosa-to-mucosa suturing is possible (See supplementary Table S6.18) [452, 453]. In case of excessive dead space after resection of the fibrosis, gracilis muscle [469] or omental flaps (laparoscopically harvested if urethroplasty was performed using perineal approach only) [431, 465] have been advised to fill up this space and support the anastomosis. These flaps, or alternatively bulbospongious muscle or local subcutaneous dartos flaps, are also useful to separate the suture lines in case of a concomitant recto-urethral fistula [431, 442, 446, 469]. If the urethra cannot be anastomosed in a tension-free fashion, despite the aforementioned manoeuvres, or in cases of ischemic narrowing/necrosis of the bulbar urethra, options are a tubed preputial island flap, staged BMG urethroplasty with flap, staged buccal mucosa dartos flap, radial forearm free flap urethroplasty or entero-urethroplasty [442, 467, 471, 473]. In case of entero-urethroplasty, the sigmoid colon is preferred above ileum (which is in turn better than stomach) because of the proximity of the vascular pedicle to the perineum. Entero-urethroplasty should only be done in the presence of a competent bladder neck because subsequent implantation of an AUS is nearly impossible [473].

Patency rate of different types of ReDo-urethroplasty varies between 50-100% (Table 6.11) [442, 463, 467, 468, 471, 473]. An alternative is to abandon the normal urinary outlet and opt for Mitrofanoff-vesicostomy, PU (if local perineoscrotal skin is suitable) or permanent suprapubic diversion [467, 473].

Table 6.10: Outcome of different types of ReDo-urethroplasty

Study	Type	N	Follow-up (months)	Patency rate
Bhagat *et al*. [471]	Progressive perineal EPA	28	29 (12-108)	36 (83,72%)
	Transpubic EPA	12		
	Tubed preputial flap	1		
	Staged BMG + local flap	2		
Fu *et al*. [468]	Progressive perineal EPA	55	36 (18-47)	33 (60%)

Garg *et al*. [467]	Progressive perineal EPA	40	31 ± 11	30 (75%)
	Transpubic EPA	2	25	2 (100%)
	Tubed preputial flap	1	25	1 (100%)
	Staged BMG + local flap	2	17	1 (50%)
	Radial forearm free flap	1	15	1 (100%)
Sa *et al*. [463]	Progressive perineal EPA	102	35 (6-63)	93 (91.2%)
Kulkarni *et al*. [442]	Progressive perineal EPA	541	68 (12-240)	412 (79.1%)
	Tubed preputial flap	37		30 (81%)
	Staged BMG flap	10		6 (60%)
	Staged BMG + local flap	15		13 (86.6%)
	Entero-urethroplasty	2		2 (100%)
	Radial forearm free flap	3		3 (100%)
	Pedicled anterolateral thigh flap	1		1 (100%)
Mundy *et al*. [473]	Entero-urethroplasty	11	NA	7 (63.6%)

BMG = buccal mucosa graft; EPA = excision and primary anastomosis; N = number of patients; NA = not applicable.

Summary of evidence	**LE**
The best results are obtained after the 1st urethroplasty.	4
The overall stricture-free rate after EPA is 85.7%. By using the progressive perineal approach, a combined transpubic abdomino-perineal approach is usually not needed.	3
After failed endoluminal treatment, EPA is the standard treatment for a non-obliterative stenosis.	3
Both a midline and inverted U perineal incision equally gain access to the posterior urethra, but a midline incision is associated with less anatomical damage to local vessels and nerves, reduced risk of surgical site infection and hospital stay.	2b
Total pubectomy during transpubic abdomino-perineal reconstruction has a higher complication rate (bleeding, pelvic instability, dead space) compared to partial (superior or inferior) pubectomy with no gain in surgical exposure.	4
By using the progressive perineal approach, a combined transpubic abdomino-perineal approach is usually not needed except for very long distraction defects and in case of complicated situations, which include associated para-urethral bladder base fistula, trauma-related recto-urethral fistula, and bladder neck injury.	3
If the urethra cannot be anastomosed in a tension-free fashion or in case of ischaemic narrowing/ necrosis of the bulbar urethra, options are a tubed preputial island flap, staged buccal mucosa graft urethroplasty with flap, staged buccal mucosa dartos flap, radial forearm free flap urethroplasty or entero-urethroplasty.	3
In case of excessive dead space after resection of the fibrosis, local flaps have been advised to fill up this space and support the anastomosis. These flaps are also useful to separate the suture lines in case of a concomitant recto-urethral fistula.	3

Recommendations	**Strength rating**
Perform open reconstruction for post-traumatic posterior stenosis only in high-volume centres.	Weak
Perform progressive perineal excision and primary anastomosis (EPA) for obliterative stenosis.	Strong
Perform progressive perineal EPA for non-obliterative stenosis after failed endoluminal treatment.	Strong
Perform a midline perineal incision to gain access to the posterior urethra.	Strong
Do not perform total pubectomy during abdomino-perineal reconstruction.	Strong

Reserve abdomino-perineal reconstruction for complicated situations including very long distraction defect, para-urethral bladder base fistula, trauma-related recto-urethral fistula, and bladder neck injury.	Weak
Perform another urethroplasty after 1st failed urethroplasty in motivated patients not willing to accept palliative endoluminal treatments or urinary diversion.	Weak
Use a local tissue flap to fill up excessive dead space or after correction of a concomitant recto-urethral fistula.	Weak

7. DISEASE MANAGEMENT IN FEMALES

7.1 Signs and symptoms of female urethral strictures

The symptoms of female urethral strictures are non-specific and therefore generally non-diagnostic. Female urethral stricture presents with mixed filling and voiding symptoms with frequency in 63%, urgency in 55%, incomplete emptying in 36%, poor flow in 32%, urinary incontinence in 31% (stress, urge or mixed), strain void in 21.5%, UTI in 20.5%, nocturia in 20.5% and dysuria in 20%. It very rarely presents with urethral pain (2.7%), terminal dribble (2%), haematuria (1.6%) or renal failure (0.5%) (see supplementary Table S7.1).

There is often a significant delay in diagnosis of FUS from time of development of symptoms with mean delays of 4.3-12 years described (range 1-30 years) [137].

7.2 Diagnosis of female urethral strictures

Twenty-four studies detail investigations leading to a diagnosis of FUS (see supplementary Table S7.2). In all cases a full history was taken, and a detailed pelvic examination was performed to assess for prolapse, masses, scars and vulval dermatological disorders such as LS, lichen planus or vulvo-vaginal atrophy. Flow rate and US PVR assessment was evaluated in nineteen (75%) and eighteen (71%) studies, respectively. Lateral VCUG was performed routinely in sixteen studies (63%) and as required in one study (4%). Cystourethroscopy was performed routinely in fourteen studies (54%) and as required in two studies (8%). Urodynamics (UDS) were performed routinely in four studies (17%) and as required in seven studies (30%) whilst video-urodynamics (VUDS) were performed routinely in three studies (13%) and urethral calibration also in four studies (13%). Pelvic MRI was performed as required in four series (17%) whilst transrectal US (TRUS) and renal US were each performed routinely in two series (8%) and intravenous urography (IVU) in ten (4%).

Flow rate and PVR assessment make inherent sense as initial non-invasive screening tools and allow for simple monitoring of effect of treatment. Voiding cystourethrography and/or VUDS will permit diagnosis of BOO [23, 474], visualisation of ballooning above the proximal end of the FUS [135], and delineation of alternate or co-existent diagnoses such as detrusor overactivity (DO) and SUI [128], although VCUG, VUDS and UDS require the ability to insert a 6 Fr catheter and may not be possible without preliminary urethral dilatation in all cases of FUS [475]. Likewise, passage of a cystourethroscopy will require a preliminary dilation in the majority of cases even when a paediatric uretero-renoscope is utilised [126]. Cystourethroscopy will allow for formal identification of the distal end of the FUS and will also allow for exclusion of a functional cause of BOO [135]. Magnetic resonance imaging is performed mainly to exclude alternate pathology such as urethral diverticulum and urethral carcinoma and also allows assessment of the degree of urethral fibrosis associated with FUS [475]. Proponents of TRUS utilise it in lieu of MRI and also for visualisation of the dilated urethra above the proximal end of the FUS. Recent gel-infused USS has been assessed and found to more accurate means of diagnosing stricture and associated spongiofibrosis than cystoscopy and videourodynamics in a small preliminary study (n=8) [476].

7.3 Treatment of female urethral strictures

*7.3.1 **Minimally invasive techniques for treatment of female urethral strictures***

Several minimally invasive treatments have been reported; these include urethrotomy, dilatation, meatotomy and meatoplasty. Meatotomy and meatoplasty are essentially the same procedure in the female urethra and the term ‘meatoplasty’ will be used throughout this document.

7.3.1.1 Urethrotomy for treatment of female urethral strictures

No papers were found detailing the use and outcomes of urethrotomy specifically for the management of FUS. Internal urethrotomy or dilation was used by Massey and Abrams [477] to treat a variety of pathologies,

including FUS, causing symptoms of obstructed voiding, and resulted in symptomatic improvement in 80% of patients. As this study included women with a variety of complaints and did not assess urodynamic parameters, the results in the patient subset with true urethral stricture are unclear. If utilised, urethrotomy in the female urethra involves incisions at three, nine and occasionally twelve o'clock [477].

7.3.1.2 Urethral dilatation for treatment of female urethral strictures

With this treatment, the urethra is dilated to between 24 Fr and 41 Fr. Some patients will continue with ISD. Romman *et al*., 2012 [478] and Popat & Zimmern [475] also described suture plication of bleeding areas of the meatus if required post-urethral dilatation.

Four studies described the results after twelve to 59 months follow-up of, in total, 183 patients having dilatation only. Patency rates ranges from 7.5-51% (see Table 7.1) [128, 129, 475, 478]. In another four studies that included, in total, 31 patients that continued to perform ISD, stabilisation of the stricture with "patency" was obtained in 37.3-100% of cases at twelve to 21 months of follow-up (see Table 7.1) [13, 133, 136, 479].

New onset SUI (1.4%) and other complications are very rare after dilation (see supplementary Table S7.3). Due to the low complication rate, the minimally invasive nature of the technique and the reasonable success rate, it is acceptable to start with urethral dilation as a first-line treatment for an uncomplicated FUS. If the stricture recurs then repeat urethral dilatation is unlikely to be curative.

7.3.1.3 Meatoplasty for treatment of female urethral strictures

Meatal stenosis is extremely rare, with only 2/58 (3%) of females evaluated for voiding dysfunction found to have true meatal stenosis [480]. Only one meatoplasty paper contains more than five patients and has been included for analysis (see supplementary Table S7.4) The patency rate of meatoplasty in girls in this paper is excellent with 96% of the 50 girls in Heising's series having a successful outcome with no reported side effects at twelve months. Forty-eight of 50 patients experienced resolution of their recurrent UTIs and improved voiding symptoms one year after meatoplasty [481]. There was no incontinence or other acute complications reported. For short meatal strictures, meatoplasty is the first-line treatment option.

7.3.2 ***Urethroplasty for treatment of female urethral strictures***

Twenty-five papers report the outcomes of urethroplasty for FUS disease in 253 patients in total after the scope search of the Panel. The Panel have analysed the outcomes of these urethroplasty according to flap or graft type as: vaginal graft, vaginal flap, labial/vestibular graft, labial/vestibular flap and buccal or lingual graft. In female urethroplasty, a dorsal approach is via a stricturotomy at twelve o'clock, a ventral approach is via a stricturotomy at six o'clock and circumferential is a full circumference reconstruction.

7.3.2.1 Vaginal graft augmentation urethroplasty for treatment of female urethral strictures

There were five studies reporting vaginal graft urethroplasty containing 72 patients. All 72 vaginal graft urethroplasties were performed via a dorsal approach in women with a mean/median age of 47.5-60.6 years (range 28-79). At a mean/median follow-up time of 8.5-24.65 months (range 6-36) following vaginal graft urethroplasty 59 (82% range 73-94%) of patients had no recurrent stricture. No complications and no new onset urinary incontinence were reported. Mean/median flow rate (with range) improved from 6.2-8.23 mls/s (2.2-10.2) to 16.64-27.6 ml/s (12-32.7) whilst mean/median PVR (with range) reduced from mean/median 113.2-187.1 mls (44-420) to mean/median 20-90.31 mls (0-122).

See supplementary Table S7.5 for further information.

7.3.2.2 Vaginal flap augmentation urethroplasty for treatment of female urethral strictures

Vaginal flap urethroplasty was reported in 150 women and was always via a ventral approach, utilising an inverted U vaginal flap inlay in seven studies (n=96) [127, 128, 131, 482, 483], a lateral C vaginal flap in three studies (n=58) [125, 133, 137] and one vaginal island flap urethroplasty in one patient [131]. At a mean/median follow-up time of 12- 80.7 months (range 3-198), patency rates of 67-100% were reported (Table 7.1). Eight (5.3%) patients had a simultaneous pubo-vaginal sling (PVS), four (2.7%) had a simultaneous Martius fat pad flap interposition and one (0.7%) had a simultaneous excision of urethral diverticulum. Fourtheen (9.3%) patients developed new onset UI, and fourtheen (9.3%) developed other acute complications including UTI and intravaginal direction of the urinary stream.

See supplementary Table S7.6 for further information.

7.3.2.3 Labial/vestibular graft augmentation urethroplasty for treatment of female urethral strictures

There were four papers detailing the outcomes of 42 patients having labial or vestibular graft urethroplasty (see supplementary Table S7.7); fifteen had ventral labial minora graft [132, 139, 484] and thirteen had dorsal labia minora graft [136] and fourtheen had dorsal labia majora graft. At a mean follow-up of 18 to 24 months, patency rates of 75-86% were reported with ventral grafting whilst this was 100% with dorsal grafting at twelve to ninetheen month's follow-up (Table 7.1). One (2.4%) ventral graft patient developed an UTI post-surgery. There were no other complications (including UI). Post void residual volume reduced from 141.9 +/- 44.2 mls to 24.5 +/- 2-.9 ms post dorsal onlay labial minora graft urethroplasty.

7.3.2.4 Labial/vestibular flap urethroplasty for treatment of female urethral strictures

There were two papers detailing the outcomes of twenty-one patients having labial/vestibular flap urethroplasty: seventeen had a dorsal vestibular flap [16], whilst twelve had a dorsal labia minora flap [485]. At a mean/median follow-up of 24 months the two ventral flap patients (100%) remained stricture-free whilst fifteen (88%) dorsal flap patients remained stricture-free at a mean of twelve months follow-up (Table 7.1 and supplementary Table S7.8). There were no adverse short- or long-term effects reported in either group.

7.3.2.5 Buccal and lingual mucosal graft augmentation urethroplasty for treatment of female urethral strictures

There were eleven papers detailing the outcomes of 234 patients, all treated with BMG except in the series of Sharma *et al*., who used lingual mucosa graft (LMG) in fifteen patients at the dorsal urethra [126]; 44 patients with dorsal onlay oral (buccal or lingual) mucosa graft (DOOMG) [126-128, 131, 134, 474, 486-488]; 27 with ventral onlay BMG (VOBMG) [127, 135, 489, 490]. The outcome of circumferential BMG urethroplasty in two patients were only detailed in one paper [127]. At a mean/median follow-up of six to 33 months, 62.5-100% of DOOMG urethroplasty patients were stricture-free whilst 92-100% of VOBMG patients were stricture-free at a mean of six to 24.5 months follow-up. Both circumferential BMG patients were stricture-free at a mean of 21 months follow-up (Table 7.1). Twenty-four (10.7%) DOOMG patients suffered a low-grade short-term adverse effect and no patients in any subgroup developed new onset UI. No patients developed acute complications or new onset stress urinary incontinence following VOBMG urethroplasty or circumferential BMG urethroplasty (although this was only performed in two patients). Mean/median flow rate improved from 5.0-12.5 ml/s (range 3-11.2) to 12.1-28 ml/s (range 14-37) and mean/median PVR reduced from 101-270 mls (range 90-200) to 6.5-122.6 mls following DOBMG. Likewise mean/median flow rate improved from 5.1-7.6 ml/s (range 3-11.2) to 18-29.2 ml/s (range 5-33.4) whilst mean/median post void residual reduced from 100-149 ml (range 0-300) to 15-59.2 ml (range 0-360 mls) following VOBMG. The flow rate and post void residual changes following circumferential BMG urethroplasty have not been detailed as this technique was performed in two patients only and the outcomes detailed in the describing paper are not specific to this technique.

One prospective randomized trial compared VOBMG with DOBMG and found equivalent stricture free rates and improvements in maximum flow rate, post void residual and sexual function. However, there were only twelve patients in each group and follow-up was limited to six months [491].

For further information see supplementary Tables S7.9, S7.10 and S7.11.

7.3.2.6 Anastomotic urethroplasty

Anastomotic urethroplasty has only been described in two cases in the literature – both in women with very short mid-urethral stricture and both of whom were stricture-free at four and 24-months follow-up respectively. None of them suffered from UI post-operatively [127, 496] (see supplementary Table S7.12).

Table 7.1: Summary of available evidence on treatment of female urethral strictures

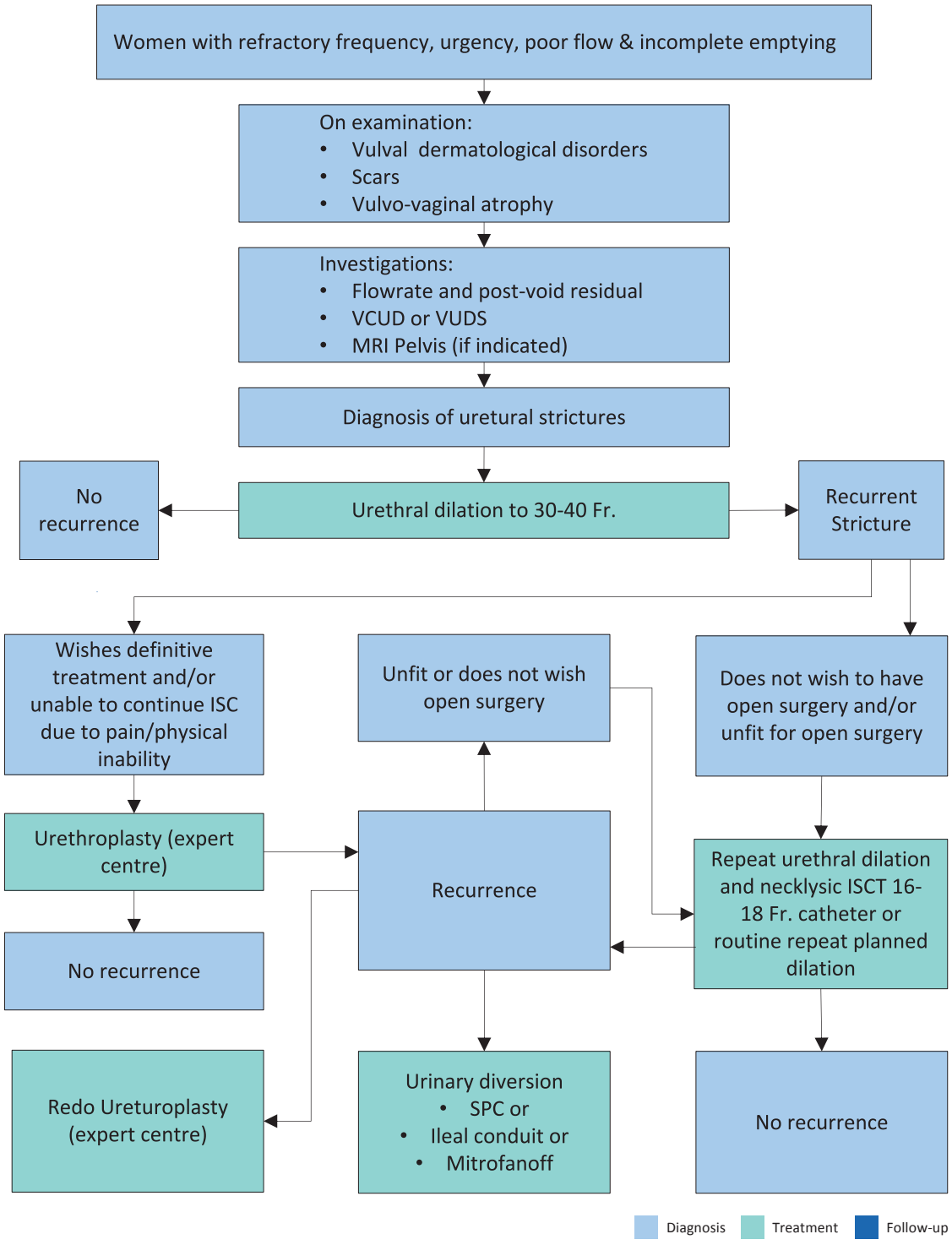
Treatment	No. of studies	No. of Patients	Patency rate (range %)	New Onset UI (%)	Mean/Median FU Months	Refs
Urethral Dilatation	6	257	40.1 (7.5-51)	1.4	12-59	[128, 129, 475, 478]
Urethral Dilatation + ISD/ planned repeat dilatation	4	109	97 (57-100)**	0	6-21	[13, 133, 136, 479]
Dorsal Vaginal graft urethroplasty	5	72	73-100	0	82 (73-94)	[15, 487, 492, 493]
Ventral Vaginal flap urethroplasty	9	150	83 (67-100)	9.3	12-80.7	[125, 127, 128, 131, 133, 137, 482, 483]
Ventral Labial/Vestibular graft urethroplasty	2	15	80 (75-86)	2.4	18-24	[132, 139, 484]
Dorsal Labial/Vestibular graft urethroplasty	2	27	100	0	12-19	[136]
Dorsal Labial/ Vestibular flap urethroplasty	21	2915	93 (88-100)	0	6-1512	[16]
Dorsal BMG urethroplasty	119	2344	81.6 (62.5-100)	2.1	6-3328	[126-128, 131, 134, 486, 474, 487, 488]
Ventral BMG urethroplasty	54	8927	93 (92-100)	0	610-24.5	[127, 135, 489, 490]

FU = follow-up; ISD = intermittent self-dilatation; N = number of patients; UI= urinary incontinence.
** Patent urethra NOT stricture free as ISC or urethral dilatation continues.*

Summary of evidence	LE
Female urethral stricture symptoms are long standing and non-specific, the most commonly reported are frequency, urgency, poor flow, incomplete emptying, and urinary incontinence. It is important to exclude FUS in female patients with LUTS.	3
Urethral dilatation alone to 24-41 Fr provides low stricture-free rates of mean 40.1% at mean follow-up 36 (12-59) months.	3
Isolated repeat dilatation yields patency rates of 26.6%. However, urethral dilatation followed by ISD or regular planned dilatation, as palliation, provides patencyrates of 97% at mean FU 6-21 months.	3
Urethroplasty provides patency rates of 62.5-100%. VOBMG and DOBMG reported patency rates are 92-100% and 62.5-100%, respectively.	3
Meatotomy/meatoplasty for short meatal strictures has a success rate of 97% at twelve months follow-up.	3

Recommendations	Strength rating
Perform flow rate, post-void residual and voiding cystourethrogram or video-urodynamics in all women with refractory lower urinary tract symptoms.	Strong
Perform urethral dilatation to 24-41 Fr as initial treatment of female urethral stricture (FUS).	Weak
Perform repeat urethral dilatation and start planned weekly intermittent self-dilatation (ISD) with a 16-18 Fr catheter for the 1st recurrence of FUS, or plan repeat dilatation.	Weak
Perform urethroplasty in women with a 2nd recurrence of FUS and who cannot perform ISD or wish definitive treatment. The technique for urethroplasty should be determined by the surgeon's experience, availability and quality of graft/flap material and quality of the ventral versus dorsal urethra.	Strong
Treat meatal strictures by meatotomy/meatoplasty.	Weak

Figure 7.1: Women with refractory frequency, urgency, poor flow and incomplete emptying



ISC = intermittent self-catheterisation; MRI = magnetic resonance imaging; VUDS = video-urodynamics.

8. DISEASE MANAGEMENT IN TRANSGENDER PATIENTS

8.1 Treatment of strictures in trans men

In trans men, stricture treatment depends on the time after neophallic reconstruction, stricture location, stricture length and quality of local tissues tissues [147, 494].

8.1.1 Management of strictures early after neophallic reconstruction

Urethral surgery on tissues in the acute phase urethra has been stabilised. This usually takes six months [495]. Endoscopic incision for short (< 3 cm) urethral strictures has been performed, mainly at the anastomotic site, with a maximum stricture-free rate of only 16.7% when performed within six months after neophallic reconstruction [496]. Insertion of a suprapubic catheter is the first-line treatment in cases of obstructive symptoms severely affecting the patient's QoL, recurrent UTI or retention. The alternative is perineostomy, which is a specialist procedure and should be performed by a urologist familiar with transgender urethral anatomy. The perineostomy may be closed at the time of formal urethral reconstruction [497].

8.1.2 Treatment of meatal stenosis in trans men

Intermittent urethral dilatation is an option as palliative treatment for low-grade meatal stenosis [31]. Patients with high-grade meatal stenosis, those who refuse ISD, or those who want a durable solution should be offered simple meatotomy. Patency rates are 50% and 75% for transmasculine after respectively metoidioplasty and phalloplasty [147]. The drawback is that the meatus will be in a hypospadiac position. Alternatively, a staged urethroplasty can be offered [147].

8.1.3 Treatment of strictures at the neophallic urethra

The standard treatment for these strictures is staged urethroplasty with or without graft augmentation (BMG or full thickness SG). A patency rate of 50-88% [147, 495, 498] has been reported after phalloplasty and up to 100% after metoidioplasty [147, 495].

For complex (e.g., fully obliterated) or recurrent strictures at the neophallic urethra, a complete urethral substitution with a tubularised radial forearm free flap has been proposed with a 67% patency rate [147].

8.1.4 Treatment of strictures at the anastomosis neophallic urethra-fixed part of the urethra

Short, non-obliterative, strictures can be treated by endoscopic incision. A first endoscopic incision has a 37-45.5% patency rate, but this dropped to 0% in case of three or more attempts (median follow-up of 51 months) [495, 496]. Therefore, repetitive endoscopic incisions should be discouraged unless with palliative intent.

For very short (< 1.5 cm) low-grade strictures, Heineke-Mikulicz urethroplasty is an option reporting a 58-80% after phalloplasty and up to 100% after metoidioplasty [147, 495].

If the stricture is nearly or completely obliterative, options are EPA, graft augmentation urethroplasty or staged urethroplasty. Excision and primary anastomosis yields a patency rate of 46-57% after phalloplasty and 78% after metoidioplasty [147, 495]. Alternatively or if EPA is not possible (stricture length >2 cm), a graft augmentation urethroplasty can be performed with a 56-100% patency rate [147, 495]. In case of insufficient ventral tissue during graft urethroplasty, it is advised to support this graft by a local fasciocutaneous flap [147]. An alternative (especially after failure of the previous techniques) can be a staged approach [147, 495].

8.1.5 Treatment of strictures at the fixed part of the urethra

This part of the urethra has a more reliable blood supply, and the dorsal part of the urethra is supported by the corporal bodies of the clitoris. Therefore, single-stage dorsal inlay graft urethroplasty is possible for strictures at this site, especially after metoidioplasty, with up to 100% patency rate [495]. Staged repair with or without a dorsal graft is an alternative for these rare strictures [495].

8.1.6 Definitive perineostomy in trans men

Definitive perineostomy should be offered to patients with refractory strictures or to those with strictures who do not wish to have complex reconstructive surgery [147, 495].

8.2 Peri-operative care after treatment of strictures in trans men

Anecdotally, after endoscopic incision and urethroplasty, the urethral catheter is maintained for two to three weeks [496, 499]. Peri-catheter urethrography is advised before catheter removal as it might be challenging to reinsert the urethral catheter in case of urinary extravasation [499].

8.3 Strictures in trans women

It is acceptable to start with dilation of a short and non-obliterative stricture in trans women although no long term data about the effectiveness are available [31]. If this is not possible or if it fails, a short (< 1 cm) meatal stricture can be treated by Y-V meatoplasty with an 85% stricture-free rate [500]. Somewhat longer (1-2 cm) meatal strictures can be treated by a neovaginal advancement flap (inverted U or "7-flap") with no recurrence observed after 37 months median follow-up [501].

Summary of evidence	LE
After neophallic reconstruction, local tissues go through the different stages of wound healing and stable wound healing is usually achieved after six months.	3
After two attempts, endoscopic incision is no longer successful in trans men.	3
Two-stage urethroplasty for strictures at the neophallic urethra has a patency rate of 50-88% after phalloplasty and up to 100% after metoidioplasty.	3
Y-V meatoplasty for short (< 1 cm) meatal stenosis in trans women has a stricture-free rate of 85%.	3

Recommendations	Strength rating
Do not perform endoscopic incision or urethroplasty within six months after neophalloplasty.	Strong
Do not perform more than two endoscopic incisions for strictures in trans men unless with palliative intent.	Strong
Perform staged urethroplasty for strictures at the neophallic urethra if open reconstruction is indicated.	Weak
Perform Y-V meatoplasty for short (< 1 cm) meatal stenosis in trans women if open reconstruction is indicated.	Weak

9. TISSUE TRANSFER

9.1 Comparison of grafts with flaps

One small RCT (LS excluded) comparing OMG with PSF found no significant difference in urethral patency rate [502]. Penile skin flaps had a higher urogenital morbidity (superficial penile skin necrosis, penile torsion, penile hypoesthesia, and post-void dribbling) and longer operation time compared to OMG. Furthermore, patient dissatisfaction was significantly higher with penile flaps [502]. Another small RCT (LS excluded) comparing penile skin grafts with PSF confirmed these findings with longer operation time and more superficial penile skin necrosis in the group of the flaps, whereas the urethral patency rate was similar between both groups [355]. Several retrospective series also found a comparable urethral patency rate between PSF and grafts [272, 274, 503, 504] (Table 9.1).

Table 9.1: Comparative studies of grafts vs. flaps used in urethroplasty for anterior urethral strictures

Study	Type of study	LS	Follow-up (months)	Flap		Graft		p-value*
				Type	Urethral patency	type	Urethral patency	
Barbagli *et al.* [272]	Retrospective	Excl.	55	LIF	12/18 (67%)	OMG/PSG	36/45 (80%)	0.32
Dubey *et al.* [502]	RCT	Excl.	22-24	LIF	22/26 (84.6%)	BMG	24/27 (88.9%)	0.70
Fu *et al.* [274]	Retrospective	Excl.	>12	All types	166/199 (83.4%)	LMG	80/94 (85.1%)	0.71

Hussein *et al.* [355]	RCT	Excl.	36	TIF	15/19 (78.9%)	PSG	13/18 (72.2%)	0.25
Lumen *et al.* [504]	Retrospective	NR	42-43	All types	23/29 (79.3%)	OMG/PSG	63/75 (84%)	0.57
Sa *et al.* [503]	Retrospective	Excl.	28 (18-60)	TIF	28/34 (82.3%)	BMG	67/82 (81.7%)	0.851

BMG = buccal mucosa graft; Excl. = excluded; LIF = longitudinal island flap; LMG = lingual mucosa graft; LS = lichen sclerosus; mo = months; NR = not reported; OMG = oral mucosa graft; PSG = penile skin graft; TIF = transverse island flap; RCT = randomized controlled trial.
** if not reported: recalculated by EAU Urethral Strictures Panel with chi²-statistics.*

Due to their robust vascular pedicle, flaps can be used as a tube as well as a patch in a single-stage approach [442]. Castagnetti *et al.*, showed that grafts used as a tube have significantly higher complication rates as compared to onlay grafts (OR: 5.86; 95% CI: 1.5-23.4) [505]. A review by Patterson *et al.*, also reported high (circa 50%) complication and recurrence rates for tubularised grafts [506]. Iqbal *et al.*, have shown an encouraging 87% stricture-free rate in 23 patients who were offered single-stage circumferential skin flap urethroplasty [281]. Therefore, if there is a need to reconstruct a complete urethral segment with a tissuetransfer tube in a one-stage operation, flaps are usually the preferred option. As flaps carry their own vascular supply to the reconstruction site, they do not rely on the local vascularisation of the recipient site. Therefore, they need to be considered in case of poor urethral vascularisation (e.g., after irradiation or dense scarring after previous urethroplasty) [504, 507]. In addition, flaps survive well in the presence of active urinary infection [508].

Grafts and flaps should not be considered competitors in urethral surgery. A combination of a flap with a graft is possible for complex, multifocal or penobulbar strictures [504, 509, 510].

Summary of evidence	**LE**
Flaps have a higher urogenital morbidity, but a comparable patency rate compared to grafts.	1b
Grafts have a significantly higher complication rate compared to flaps when complete tubularisation in a single-stage approach is needed.	1b
Flaps do not rely on the local vascularisation of the recipient site.	3

Recommendations	**Strength rating**
Use a graft above a flap when both options are equally indicated.	Strong
Do not use grafts in a tubularised fashion in a single-stage approach.	Strong
Use flaps in case of poor vascularisation of the urethral bed.	Weak

9.2 Comparison of different types of flaps

Different local flaps have been described. Penile skin flaps are generally hairless, although the ventral penile skin can be hair-bearing around the raphe in some ethnic groups/phenotypes. They can be harvested as a transverse preputial skin flap [511], a transverse distal PSF [358, 508, 512, 513] or as a longitudinal island flap [514]. Urethral patency rates vary between 74.2-100% [274, 358, 508, 511-514]. Complications include skin necrosis (0-3.8%), fistula (0-7%), penile deformity (0-7%), post-void dribbling (0-79%) and sacculation (0-16.5%) (see supplementary Table S9.1). As there are no direct comparative series available about these flaps it is not possible to determine which performs better.

Hair-bearing perineal and scrotal flaps have been described as well. Fu *et al.*, demonstrated that PSF had a significantly better urethral patency rate compared to scrotal and perineal skin flaps (respectively 87.7%, 69% and 66.7%) [274]. The hair-bearing perineal and scrotal skin flaps are associated with hairball formation and chronic infection which may cause failure of the repair. A study of Blandy with long-term follow-up, reports 3% revision for calculi and 3% revision for diverticula [515].

An alternative is to epilate the needed scrotal skin prior to tissue transfer [516, 517] or to patch an OMG to the underlying dartos tissue of the scrotum after incision of the scrotal skin and use this patch as a flap in a second attempt [442].

Summary of evidence	LE
Hair-bearing flaps have a lower urethral patency rate compared to non-hair-bearing flaps.	3

Recommendation	Strength rating
Do not use hair-bearing perineal or scrotal flaps unless no other option is feasible.	Strong

9.3 Comparison of different types of grafts

Buccal mucosa is at present the most commonly used graft. A systematic review on anterior urethral strictures reports a urethral patency rates of buccal mucosa of 86.6% with an average follow-up of 31.5 months [518].

Penile skin is another popular graft, especially in uncircumcised men where the foreskin is an abundant source of graft material.

In case of LS, Trivedi *et al*., demonstrated a significantly higher urethral patency rate when using non-genital mucosal grafts for reconstruction (82.6%) compared to genital skin grafts (4%) [519]; therefore, the use of genital skin in LS cases is not indicated.

In one RCT (Pee'BuSt trial) comparing buccal mucosa with penile skin as a graft for dorsal onlay augmentation urethroplasty for anterior strictures, no significant difference in outcome could be observed [520]. A systematic review and meta-analysis suggests that BMG augmentented urethroplasty, may be superior to penile skin graft urethroplasty. However, there were a lot of confounding factors, and clear conclusions cannot be made [521]. Lengthy skin grafts (up to 20 cm) can be taken from the foreskin in a spiroid fashion which is clearly more difficult with OMG.

The main disadvantage of BMG harvesting is the oral morbidity and because of this morbidity, lingual mucosa has been proposed as alternative. A SR and meta-analysis of comparative studies comparing LMG with BMG (four prospective, two retrospective studies) showed no significant differences in urethral patency rate and overall long-term complication rate [522-524]. These studies revealed that LMG was associated with more difficulties in eating/drinking, speaking, tongue protrusion and dysgeusia [522, 523]. In 13.8-20%, speaking problems remained after six months [522, 523]. A retrospective study of Xu *et al*., reported difficulties in tongue movements, numbness over the donor site and speaking difficulties in 6.2%, 4.9% and 2.5% of patients, respectively after twelve months [301]. On the other hand, BMG harvesting provoked more oral tightness which was present in up to 24% of patients after six months [522, 523]. Chauhan *et al*., showed that immediate and early donor site complications were more common in the BMG group, except for bleeding being more common in the LMG group. Numbness (61%), difficulty in chewing (54%), swelling (48%) and articulation (40%) were the most common problems during the first week. Late donor site complications were rare [525]. Pal *et al*., describes more short-term complications (difficulty in tongue movement and slurring of speech) in the LMG group, compared to the BMG group. Long-term complications (after three months) at the donor site (persistent pain, perioral numbness, tightness of mouth, salivary disturbance, scarring of the cheeks) were only seen in the BMG group [526]. For long strictures, buccal mucosa can be combined with lingual mucosa [301].

The use of lower lip mucosa was described, especially when smaller grafts are needed, and has similar qualities to lingual mucosa. However, a narrative review based on the experience from retrospective series showed that these grafts have a higher post-operative donor site morbidity and can lead to permanent sequelae (persistent discomfort, neurosensory deficits, salivary flow changes and important aesthetic changes) at the donor site, which have not been described with lingual mucosa [527].

Beyond the oral mucosa and penile skin graft, a multitude of other autologous grafts have been described. These include: postauricular skin [510, 528], abdominal skin [360], split-thickness mesh graft from the thigh [341], inguinal skin [300] and colonic mucosa [529] (Table 9.2). Manoj *et al*., only used the postauricular skin when both genital skin and oral mucosa were not usable [528]. Marchal *et al*., used postauricular skin in addition to oral mucosa to reconstruct lengthy strictures [510]. Meeks *et al*., reported the use of abdominal skin graft mainly in patients with lengthy strictures where OMG harvesting would be insufficient, in case of prior OMG urethroplasty or if OMG was refused by the patient [360]. Pfalzgraf *et al*., reported a comparable urethral patency rate for split-thickness mesh graft and BMG (respectively 84 and 83%), but more penile deviation (9% vs. 0%) and lower satisfaction (83.3% vs. 96.7%) with split-thickness mesh graft [341]. Xu *et al*., used colonic mucosa for lengthy (> 10 cm) strictures. Urethral patency rate was 85.7% but graft harvest requires an abdominal procedure, and 1/35 (2.9%) patient developed a colonic-abdominal fistula [529]. Due to the limited experience with grafts other than oral mucosa and penile skin, they should only be considered if oral mucosa and penile skin are not available, indicated, or desired.

Table 9.2: Outcome of case series of other autologous grafts

Study	Type of graft	N	Follow-up (months)	Stricture length (cm)	Urethral patency (%)
Bastian *et al*. 2012 [302]	Inguinal skin	34	70 (3-86)	8 (1.5-14)	91
Manoj *et al*. 2009 [528]	Postauricular skin	35	22 (3-48)	8.9 (3-15)	89
Meeks *et al*. 2010 [360]	Abdominal wall skin	21	28 (11-52)	11 (4-24)	81
Pfalzgraf *et al*. 2010 [351]	Split thickness skin graft	57/68	32	NR	84
Xu *et al*. 2009 [529]	Colonic mucosa	35	53.6 (26-94)	15.1 (10-20)	85.7

N = number of patients; NR = not reported.

Summary of evidence	LE
Patency rates of buccal mucosa and lingual mucosa are comparable.	1a
Different types of oral grafts have distinct types of oral morbidity and some of the oral complications might last in the long-term.	1a
Patency rates with penile skin grafts are 79-81.8% versus 85.9-88.1% with buccal mucosa.	3
In LS related strictures, the use of genital skin graft is associated with poor patency rates (4%).	3

Recommendations	Strength rating
Use buccal or lingual mucosa if a graft is needed and these grafts are available.	Weak
Inform the patient about the potential complications of the different types of oral grafting (buccal versus lingual versus lower lip) when an oral graft is proposed.	Strong
Use penile skin if buccal/lingual mucosa is not available, suitable, or accepted by the patient for reconstruction.	Weak
Do not use genital skin graft in case of lichen sclerosus.	Strong

9.4 Tissue engineered grafts

9.4.1 Cell-free tissue engineered grafts

These grafts are derived from cadaveric or animal sources (e.g., porcine small intestine submucosa [SIS], acellular bladder matrix, acellular dermal matrix), are completely cell-free and serve as a scaffold for host cell ingrowth [530]. The main advantage suggested for their use is the off-shelf availability [530].

A small RCT (n=30) comparing acellular bladder matrix with BMG reported a urethral patency rate of respectively 66.6% and 100%. The poorer results of acellular bladder matrix were the most apparent in cases of an unhealthy urethral bed [531].

Several small retrospective case series using mainly porcine small intestinal submucosa, demonstrate varying patency rates from 20-110%. The patient groups were heterogenious in terms of aetiology, previous treatment, urethral location and definition of success rate. An overview can be found in Table 9.3. Most papers report a poorer outcome in case of extensive spongiofibrosis, poor vascular graft bed, previous treatments and longer strictures [531-535] (Table 9.3).

Table 9.3: Outcome of retrospective case series using cell-free tissue engineered grafts

Study	N	FU (mo)	Type of graft	Patency Rate (%)
el-Kassaby *et al*. 2008 [531]	15	25	cadaveric acellular bladder matrix	33-88
Palminteri *et al*. 2012 [535]	30	71	porcine small intestinal submucosa	76
Xu *et al*. 2013 [534]	28	24.8	porcine small intestinal submucosa	92
Tang *et al*. 2020 [533]	49	15	allogeneic acellular dermal matrix	85.7
Fiala *et al*. 2007 [532]	50	31.2	porcine small intestinal submucosa	80

Summary of evidence	LE
Patency rate of cell-free tissue engineered grafts decreases with large stricture length and unhealthy urethral bed.	1b

Recommendation	Strength rating
Do not use cell-free tissue engineered grafts in case of extensive spongiofibrosis, after failed previous urethroplasty or stricture length > 4 cm.	Weak

*9.4.2 **Autologous tissue engineered oral mucosa graftss***

These grafts contain a matrix seeded with autologous oral mucosa cells. Production requires a small oral mucosa biopsy (at 0.5 cm²) and the graft is further manufactured in the lab. The main advantage suggested is the reduction of oral donor site morbidity whereas the main disadvantages are costs and the strict time frame between manufacturing and implantation of the graft [530].

The clinical use of autologous tissue-engineered OMG was evaluated in a prospective, multicentre study including 99 patients [536]. Estimated twelve- and 24-months urethral patency rate was 67.3 and 58.2%, respectively. Oral adverse events were minimal. No comparative studies with acellular grafts or native OMGs are available nor are there any data about the cost-effectiveness [530].

Summary of evidence	LE
Safety, patency rate and cost-effectiveness of autologous tissue-engineered grafts is currently under research.	3

Recommendation	Strength rating
Do not use autologous tissue-engineered oral mucosa grafts outside the frame of a clinical trial.	Strong

9.5 Management of oral cavity after buccal mucosa harvesting

The post-operative morbidity of closure vs. non-closure of the buccal mucosa harvesting site has been evaluated by a number of prospective RCTs.

The results are summarised in Table 9.4. Based on these findings, no clear recommendation can be provided as to whether or not to close the harvesting site and the decision can be left to the treating physician.

Oral rinsing with chamomile [537] or chlorhexidine [523, 538] solution has been suggested in the first post-operative days without any evidence that this reduces pain or other oral complications.

Table 9.4: Effect of non-closure compared to closure on oral morbidity after buccal mucosa harvesting

Study	Early oral pain	Eating/ drinking problems	Altered taste	Altered salivation	Oral tightness	Perioral numbness	Oral bleeding	Slurred speech
Soave *et al*. [537]	=	=	=	=	=	=	=	=
Rourke *et al*. [539]	=	↓	NR	NR	↓	↓	=	NR
Muruganandam *et al*. [540]	↓	=	NR	=	=	=	=	NR
Wong *et al*. [538]	=	↑	NR	NR	=	=	=	NR
Lumen *et al*. [523]	↑	NR	NR	NR	NR	NR	NR	NR

↓ = less morbidity with non-closure; ↑ = more morbidity with non-closure; = = no significant difference; NR = not reported.

10. PERI-OPERATIVE CARE OF URETHRAL SURGERY

10.1 Urethral rest

After any form of urethral manipulation (urethral catheter, ISD, dilatation, DVIU), a period of urethral rest is necessary in order to allow tissue recovery and stricture "maturation" before considering urethroplasty. This improves the ability to identify the true extent of the fibrotic segments during subsequent surgery. If the patient develops incapacitating obstructive symptoms or urinary retention, a suprapubic catheter should be inserted. Terlecki *et al*., propose diagnostic evaluation after two months and urethroplasty after three months of urethral rest. These timings are based on the general principles of wound healing [541]. In their study, it has been shown that these periods allow for reliable stricture evaluation during urethrography which is, in turn, important to ensure selection of the most appropriate urethroplasty technique [541]. Utilising this strategy, similar outcomes were obtained compared to patients with stable previously unmanipulated strictures [541]. However, the optimal duration of urethral rest for all patients is not known and the degree of associated infection and inflammation should be taken into account as well, with longer periods of rest in those with greater degrees of infection and inflammation.

Summary of evidence	LE
After any form of urethral manipulation, a minimum period of three months urethral rest is necessary to allow for tissue healing before performing urethroplasty.	3

Recommendation	Strength rating
Do not perform urethroplasty within three months of any form of urethral manipulation.	Weak

10.2 Antibiotics

Post-operative wound infection and UTI are common post-operative complications and infection at the site of reconstruction may contribute to failure of urethroplasty. The vast majority of reconstructive urologists perform urine culture one to two weeks prior to surgery [542]. Urine culture is superior to urine-analysis which can be omitted in the pre-operative evaluation [542]. If infection or colonisation is present, a therapeutic course with antibiotics is recommended pre-operatively. Preoperative UTI, even when properly treated, could increase the risk of post-operative UTI [543]. In case of an indwelling catheter general principles would suggest at least an attempt to suppress the colonisation with pre-operative antibiotics [542]. These practices are in accordance with the strong recommendations of the EAU Guidelines on Urological Infections:

- "Screen for and treat asymptomatic bacteriuria prior to urological procedures breaching the mucosa."
- "Treat catheter-associated asymptomatic bacteriuria prior to traumatic urinary tract interventions."

An intra-operative prophylactic regimen with antibiotics (according to local antibiotic resistance profiles) is effective in reducing the rate of post-operative surgical site and UTIs [542]. Although most urologists continue with post-operative antibiotics upon and even beyond catheter removal, there is no evidence that such a prolonged administration would reduce the infective complication rate [542]. A retrospective study from Baas *et al*., revealed that extended postoperative antibiotic prophylaxis (three weeks until catheter removal versus 3 days around catheter removal) does not appear to affect UTI rates following urethroplasty [544]. The EAU Guidelines on Urological Infections do not routinely recommend the use of antibiotic prophylaxis to prevent clinical UTI after urethral catheter removal. There is no evidence that this recommendation would not apply to catheter removal after urethral surgery.

Summary of evidence	LE
An intra-operative prophylactic regimen with antibiotics is effective in reducing the rate of postoperative surgical site and urinary tract infections.	4

Recommendation	Strength rating
Administer an intra-operative prophylactic regimen with antibiotics at time of urethral surgery.	Strong

10.3 Catheter management

After uncomplicated DVIU, there is no advantage in maintaining the catheter for a prolonged period and it should be removed within 72 hours [545].

After one-stage urethroplasty and closure of the urethral plate after staged urethroplasty, urinary extravasation at the site of reconstruction must be avoided [546]. For this purpose, urinary diversion by either transurethral catheter or suprapubic catheter with urethral stent can be used. With respect to the type of catheter material, a prospective randomised (but underpowered) trial comparing silicone vs. hydrogel coated latex transurethral catheters showed no significant difference in the time to stricture recurrence nor in the overall recurrence rate [546]. The size of the urethral catheter utilised usually varies between 14 Fr and 20 Fr [547, 548]. Systematic use of anticholinergic drugs has not shown a significant reduction in the rate of involuntary pericatheter voiding whilst catheterised [549].

After urethroplasty an indwelling catheter is commonly left *in situ* for two to three weeks [548, 550]. After three weeks of urethral catheterisation, an extravasation rate of 2.2-11.5% at urethrography has been reported after different types of urethroplasty [550-553]. However, success with early catheter removal under three weeks has also been reported. A study after EPA for non-complicated anterior strictures demonstrated no significant difference in extravasation (6.8% vs. 4.5%) and recurrence rates (4.9% vs. 5.2%) between catheter removal at one or two weeks respectively [554]. Poelaert *et al*., reported an extravasation rate of 3.5% vs. 8.3%, when the catheter was removed < 10 days or > 10 days respectively after all types of urethroplasty (n=219) (p=0.158) [547]. Importantly, patients who had a duration of catheterisation of > 10 days had longer and more complex strictures [547]. Beiske *et al*., revealed a higher incidence of UTI in patients with a three week catheterization after open urethroplasty, compared to two weeks [555].

Prior to catheter removal after urethroplasty, it is important to assess for urinary extravasation to avoid ensuing complications including peri-urethral inflammation, abscess formation and fistulation [550, 552]. Importantly, some authors have identified urinary extravasation as a predictive factor for stricture recurrence [547, 556]. Other series, however, could not confirm the prognostic significance of urinary extravasation but they included any form of extravasation (including minor leaks) [552, 553]. Grossgold *et al*., found that high-grade leaks (defined as length > 1.03 cm and width > 0.32 cm) were significantly associated with higher restricture rates. This study also found length of extravasation > 1.03 cm alone to be an independent predictor of restricture [556]. In cases of persistent and significant urinary extravasation, the catheter should be maintained or reinserted and the examination repeated after one week [550]. However, low-grade ("wisp-like") extravasation does not appear to affect long-term restricture rate and the catheter can be removed in these cases without subsequent urethrogram [552, 556]. In case of any doubt about the significance of extravasation, it is safe to keep the catheter in for an additional week and ReDo the assessment.

The assessment of urinary extravasation is achieved by either pericatheter retrograde urethrography (pcRUG), classic RUG or VCUG [550]. A prospective study (n=80) comparing pcRUG and VCUG in a within-patient fashion demonstrated a comparable sensitivity for contrast extravasation. Moreover, pcRUG averts the risk of having to reinsert the catheter, avoids the problem of patients being unable to void during VCUG and requires significantly less radiation (120 mGy/cm^2 versus 241 mGy/cm^2; $p < 0.001$) [557].

In cases of attempted VCUG where the patient is not able to void during fluoroscopy after catheter removal, RUG should be performed [556].

Although limited evidence for urethroplasty care in trans men exists, one study advised a three-week period of transurethral catheterisation with pcRUG upon catheter removal [499].

After perineostomy or the 1st stage of staged urethroplasty, the catheter can be removed without need for urethrography after three to five days [339, 552].

Summary of evidence	**LE**
Prior to catheter removal after urethroplasty, it is important to assess for urinary extravasation with urethrography to avoid ensuing complications including peri-urethral inflammation, abscess formation and fistulation.	2b
After uncomplicated DVIU, there is no advantage in maintaining the catheter for a prolonged period.	3
Early catheter removal may be appropriate for a subset of patients with short, uncomplicated, strictures.	3

Recommendations	Strength rating
Perform a form of validated urethrography after urethroplasty to assess for urinary extravasation prior to catheter removal.	Strong
Remove the catheter within 72 hours after uncomplicated direct vision internal urethrotomy or urethral dilatation.	Weak
Consider 1st urethrography seven to ten days after uncomplicated urethroplasty to assess whether catheter removal is possible, especially in patients with bother from their urethral catheter.	Weak

11. FOLLOW-UP

11.1 Rationale for follow-up after urethral surgery

The rationale for following-up patients after urethral stricture surgery is to detect and manage any complication or recurrence. As with any surgical procedure, following urethroplasty some patients will present with complications at short to medium follow-up: up to 34-38% of all anterior urethroplasties. Most of these complications (92-99.1%) would be classified as Clavien grade 1 or 2 [558, 559]. Even though urethroplasty techniques provide the highest chances for successful treatment of urethral strictures, some patients will experience recurrence [346]. For further details on particular outcomes in each urethral segment, please review the individual chapters of this Guideline.

Summary of evidence	LE
After urethroplasty surgery, recurrent strictures appear with different frequency depending on stricture features and urethroplasty techniques.	3

Recommendation	Strength rating
Offer follow-up to all patients after urethroplasty surgery.	Strong

11.2 Definition of success after urethroplasty surgery

The "traditional academic" definition of post-operative success after urethroplasty has been considered as "The lack of any post-operative intervention for restricture" [560]. This definition, despite being widely used [305, 558] is problematic as it ignores asymptomatic or even symptomatic recurrences in patients not willing to undergo further surgeries [560]. There is some variation as to what is considered intervention with some groups accepting endoscopic treatments as success, while considering failure only as the requirement for a ReDo urethroplasty [306].

A more objective definition of success is the "anatomic success", defined as "Normal urethral lumen during RUG or cystoscopy, regardless of patient symptoms". Using this definition, stricture recurrence or anatomical failure is considered by some groups as urethral narrowing found to be endoscopically impassable – without force – with a 16 Fr flexible endoscope [145, 561]. This definition is certainly stricter, with up to 35% of cystoscopic recurrences after bulbar urethroplasty remaining asymptomatic, and thus would have been considered as successful if a "lack of further intervention" definition was used [145]. Other groups consider cystoscopic recurrence as any stricture that is visible on post-operative cystoscopy, even the so-called "large calibre re-strictures" (> 17 Fr) [143]. Not all anatomic recurrent strictures would need further treatment [560]. It was suggested to intervene when the anatomic recurrence is associated with recurrence of symptoms, stricture-related high post-void residuals or a stricture calibre of < 14 Fr – even if these are asymptomatic [560].

Over the last ten years, the evaluation of urethral surgery outcomes has shifted towards a "patient-reported definition of success". The aim of any urethral intervention is to allow patients to return to a normal state of voiding while maintaining QoL or to minimise symptoms, reduce disability, and improve HRQoL by restoring normal urinary function [562]. Even if the surgeon reconstructed a wide and patent urethra, if patients experience pain, sexual dysfunction or perceive their urinary function as not improved, they will not rate their outcome as successful [560]. On a multivariate analysis including both patient-reported and clinical parameters, urine flowmetry parameters failed to demonstrate significant contribution to satisfaction [563]. Kessler *et al*., reported that only 78.3% of patients with clinical success described themselves as (very) satisfied. More

dissatisfaction significantly appeared with penile curvature, penile shortening, worsening of erectile function and impairment of sexual life [564]. Conversely, 80% of patients defined as clinical failures considered themselves as (very) satisfied with their outcomes [564]. Regardless of anatomic success after urethroplasty, post-operative pain, sexual dysfunction and persistent LUTS were independent predictors of patient dissatisfaction [563]. Improvement in voiding function (i.e., statistical improvement on IPSS) alone does not predict patient satisfaction after urethroplasty [565]. On a multivariate analysis including both patient-reported and clinical parameters, after adjusting for disease recurrence and age, persistence in voiding symptoms (weak stream), genitourinary pain, and post-operative sexual function alterations were the greatest independent drivers of post-operative dissatisfaction [563]. In addition, penile shortening (OR: 2.26; 95% CI: 1.39-3.69) and chordee (OR: 2.26; 95% CI: 1.44-4.19) were independent predictors of patient dissatisfaction after urethroplasty [565] (Table 11.1).

Table 11.1: Predictors of patient dissatisfaction after urethral surgery

Predictor/Symptoms	Measure of effect	Authors
Weak/very weak urinary stream	< 0.001	Kessler TM *et al*. J Urol 2002 [564]
Penile curvature	0.001	
Penile shortening	0.001	
Worsening of erectile function	0.001	
Impairment of sexual life	< 0.001	
Sexual activity alteration	OR: 4.36 (1.54 – 12.37)*	Bertrand LA *et al*. J Urol 2016 [563]
Erection confidence (SHIM)	OR: 1.53 (1.12 – 2.07)*	
Inability to ejaculate (MSHQ)	OR: 1.52 (1.15 – 2.01)*	
Urethral pain	OR: 1.71 (1.05 - 2.77)*	
Bladder pain	OR: 2.74 (1.12 – 6.69)*	
Urinary strain (CLSS)	OR: 3.23 (1.74 – 6.01)*	
Hesitancy (IPSS)	OR: 2.01 (1.29 – 3.13)*	
Voiding quality of life (IPSS)	OR: 1.96 (1.42 – 2.72)*	
Penile shortening	OR: 2.26 (1.39-3.69)**	Maciejewski CC *et al*. Urology 2017 [565]
Chordee	OR: 2.26 (1.44 – 4.19)**	

SHIM = Sexual Heath Inventory for Men; MSHQ = Male Sexual Health Questionnaire;
CLSS = Core Lower Urinary Tract Symptom Score; IPSS = International Prostate Symptoms Score.

Due to this evident discrepancy between surgeon's assessment and patient assessment, PROMs have been developed for the follow-up after urethroplasty [160, 562].

A complete approach for urethral surgery outcomes would combine both anatomic, endoscopic, and Patient-reported success [560, 566]. The Panel suggest using a functional definition of success in clinical practice, namely "lack of symptoms and/or need for further interventions".

Collecting standardised documentation of the patient's subjective assessment of their symptoms and objective anatomic outcomes would be limited for academic purposes, in order to allow comparison of surgical outcomes among reconstructive urologic surgeons and centres. Those objective and subjective outcomes measures should therefore be assessed and reported (simultaneously but separately) when evaluating urethroplasty results [560].

11.3 Follow-up tools after urethral surgery

*11.3.1 **Diagnostic tools for follow-up after urethral surgery***

11.3.1.1 Calibration during follow-up after urethral surgery

The difference between calibration and urethral dilatation is usually subjective as soft strictures may be dilated during calibration [567]; therefore, urethral calibration should be used with caution for follow-up after urethroplasty. Dedicated calibration bougies should be used and not dilatators.

11.3.1.2 Urethrocystoscopy during follow-up after urethral surgery

Urethrocystoscopy has been considered the most useful tool to confirm the presence or absence of a recurrent stricture [143, 568], as up to 35% of patients with re-strictures remain asymptomatic [145]. Also, the cystoscope could be a measure to calibrate the strictured lumen, bearing in mind the most commonly used endoscopes: 15.7 Fr (5 mm diameter) or 17.3 Fr (5.5 mm diameter) [568]. Urethrocystoscopy allows differentiation of recurrences as diaphragm/cross-bridging – responding to simple intervention, or significant urethral restrictures – requiring repeated interventions or ReDo surgeries [569]. Endoscopic assessment at three months after anterior urethroplasty can predict the risk for further re-intervention at one year. Compared to normal endoscopy, large calibre (> 17 Fr) restrictures have a HR of 3.1 (1.35-7.29) for repeat intervention while small calibre (< 17 Fr) restrictures have a 23.7 HR (12.44-45.15) adjusted for age, stricture length, location, and aetiology [143]. The main problem with using urethrocystoscopy for routine follow-up is the low compliance of patients as only 54% of patients underwent endoscopy at one year after urethroplasty, even when it was a part of a study protocol [145].

11.3.1.3 Retrograde urethrogram and voiding cystourethrogram during follow-up after urethral surgery

Retrograde urethrogram combined with VCUG are commonly used to confirm suspected recurrence [570, 571] or as part of a routine protocol to assess post-operative urethral patency [572, 573].

11.3.1.4 Urethral ultrasound – Sonourethrography during follow-up after urethral surgery

The use of SUG as a follow-up tool is not very common. It would be a reliable tool for diagnostic recurrent strictures [570].

11.3.2 ***Screening tools for follow-up after urethral surgery***

These tools are used to assess whether there is suspicion of stricture recurrence and need for subsequent diagnostic evaluation (see section 5. Diagnostic evaluation).

11.3.2.1 Flow-rate analysis during follow-up after urethral surgery

Evaluating the Q_{max} is the commonest follow-up tool. Different cut-off points from Q_{max} 15 ml/s or 12 ml/s were suggested to consider the intervention as a failure or to trigger a confirmatory test for recurrence [574]. There is no clear threshold, and 19% of patients with Q_{max} < 14 ml/s would still have a patent urethra, allowing passage of 15 Fr cystoscope [146].

Flow rates may be affected by operator error, BPO/LUTS, bladder dysfunction, and variations in bladder capacity. Further limitations of uroflowmetry include the need for a minimum voided volume of 125-150 ml to reach a voided flow rate that reliably predicts an abnormality [567]. Even in controlled settings, the percentage of patients with adequate pre- and post-operative uroflowmetry analysis is only 31% [573]. Comparing both pre- and post-operative Q_{max} levels was suggested, and a difference in Q_{max} of 10 ml/s or less is found to be a reliable screen tool for recurrence (sensitivity 92%, specificity 78%). This measure also has strong reproducibility (R=0.52) [573]. Unfortunately, this improvement after urethroplasty is significantly different between age groups, with less than 10 ml/s average change in those over 65 years old, probably affected by BPO and/or bladder dysfunction [575]. Another parameter to consider is the shape of the voiding curve, recording it as flat (obstructed) or bell-shaped [576]. An obstructive voiding curve demonstrated 93% sensitivity to predict recurrent strictures, while a combination of urinary symptoms and obstructive voiding curve achieved 99% sensitivity and 99% NPV [576].

11.3.2.2 Post-void residual ultrasound measure during follow-up after urethral surgery

Post-void residual US measure is significantly increased in patients with recurrent strictures compared with those without recurrences [570]. Unfortunately, PVR measurement is affected by abdominal ascites, bladder diverticula and/or poor bladder function [567], with some studies reporting inconsistent correlation with obstruction in the presence of BPO. Also, US measures of PVR are user dependent, showing high interobserver variability. Combined with other tests – uroflowmetry, IPSS, and SUG – PVR achieves adequate predictive values [570], but currently there is no literature to support its solo use, to assess urethral stricture recurrence [577].

11.3.2.3 Symptom questionnaires during follow-up after urethral surgery

The IPSS questionnaire, despite being designed for BPO, showed significant improvement after successful urethroplasty and inverse significant correlation with Q_{max} [565, 567]. The mean improvement of IPSS is around -11 points (range -19 to -5) [575].

Table 11.2: Post-urethroplasty changes in IPSS values

Author	N	Mean pre-operative value	Mean post-operative value	Change	Significancy
Morey AF *et al*. 1998 [578]	50	26.9	4.4	NR	p < 0.0001
DeLong J *et al*. 2013 [575]	110	NR	NR	-11 (IQR -19 - -5)	p < 0.001
Maciejewski CC *et al*. 2017 [565]	94	18.7 (+/- 9)	5.8 (+/- 5)	NR	p < 0.0001

N = number of patients; NR = not reported; IPSS = International Prostate Symptoms Score; IQR = interquartile range.

Combination of IPSS and Qmax analysis was suggested to diagnose recurrences. Using an IPSS cut-off point of 10 points associated with Q_{max} > 15 ml/s would prevent further invasive studies in 34% of patients, while only 4.3% of strictures < 14 Fr would have been missed. Using an IPSS cut-off point of 15 points associated with Q_{max} > 15 ml/s would prevent further invasive studies in 37% of cases, while 6% of strictures < 14 Fr would have been missed [579].

The Visual Prostate Symptom Score (VPSS) was also used to diagnose recurrent urethral strictures, offering a significantly shorter time to completion compared with IPSS, especially in cases of illiteracy or limited education. Visual Prostate Symptom Score showed a good correlation with IPSS, Q_{max} and urethral diameter. A combination of VPSS > 8 with Q_{max} < 15 ml/s had a NPV of 89% and a PPV of 87% for recurrent urethral strictures [580].

Post-micturition dribble, assessed by the specific question of the USS-PROM questionnaire, was present in 73% of patients pre-operatively and 40% after anterior urethroplasty, while only 6.3% was *de novo*. Incidence was not predicted by stricture location nor urethroplasty type [150].

11.3.3 Quality of life assessment, including disease specific questionnaires during follow-up after urethral surgery

Urethral stricture affects QoL evaluated by EQ-5D-3L questionnaire. Pre-operative anxiety and depression was found in 29% of patients. *De novo* AD after urethroplasty is uncommon (10%) and has two predictors: decreased sexual function and poor reported image of overall health [581]. A more recommended approach is the assessment of the condition-related QoL [582]. The USS-PROM proved useful to assess outcomes in anterior urethroplasty patients [562]. Its use also received criticism, as some of the individual generic QoL questions do not improve after successful urethroplasty, as they are not condition-specific [583]. Currently, there is another version of PROM, being developed and validated by a North American collaborative group, including questions related to the sexual consequences of urethral stricture disease [161]. PROM questionnaires should be implemented in each visit to check for functional success, as they are able to show improvement over time.

The Core Lower Urinary Tract Symptom Score (CLSS) questionnaire was used to assess pre- and post-urethroplasty pain in the bladder, penis/urethra, and perineum/scrotum. Most of the parameters improved after urethroplasty, but up to 29% of patients reported worsening of perineal pain after surgery [584].

Sexual function should be evaluated by validated tools if not assessed in a PROM. The international index on erectile function (IIEF), SHIM, O´Leary Brief Male Sexual Function Inventory (BMFSI), SLQQ (Sexual Life Quality Questionnaire), Male Sexual Health Questionnaire (MSHQ) have all been used after urethroplasties for evaluation of erectile and ejaculatory functions. Other non-validated tools were suggested such as the Post-Urethroplasty Sexual Questionnaire (PUSQ) [585] or specific questionnaires for genital appearance (length, curvature) or sensitivity [586].

Summary of evidence	LE
Retrograde urethrography and urethrocystoscopy are able to identify anatomical success after a urethroplasty.	2a
A significant gap was demonstrated between objective and subjective outcomes after urethroplasties. PROM questionnaires are specific tools to assess subjective outcomes and patient satisfaction after urethroplasty surgeries.	2a
Validated questionnaires proved useful to assess the consequences of urethral surgery on sexual function.	2a

Recommendations	Strength rating
Use cystoscopy or retrograde urethrography to assess anatomic success after urethroplasty surgery.	Weak
Use PROM questionnaires to assess subjective outcomes and patient satisfaction.	Strong
Use validated questionnaires to evaluate sexual function after urethral stricture surgeries.	Strong

11.4 Ideal follow-up interval after urethral surgery

The optimal follow-up strategy must allow for an objective determination of anatomic and functional outcomes to assess surgical success whilst avoiding excessive invasive testing that leads to unnecessary cost, discomfort, anxiety, and risk [560].

After anterior urethroplasty, 21% of recurrences are clinically evident, and cystoscopically confirmed, after three months [587] and 96% after one year [569]. Early recurrences are more frequent in patients with LS and older age, in longer strictures and when skin grafts were used [587].

11.5 Length of follow-up after urethral surgery

The median time of recurrence after bulbar urethroplasty is approximately ten months [334]. In case series, between 55.4% [587] and 96% [569, 572] of all recurrences are detected during the first year of follow-up after urethral surgery. Twenty-three percent of bulbar stricture recurrences are detected during the second year of follow-up, and the percentage of recurrences decreases after the second year [346].

On the other hand, long-term follow-up studies highlighted the role of length of follow-up as a predictor for stricture recurrence after bulbar urethroplasty [346, 588]. Late recurrences – later than five years after urethroplasty – could be observed in up to 15% of cases [144, 331, 346]. This should be considered mainly after augmentation urethroplasties, especially in case skin grafts were used [571]. Certainly, patients should be instructed to seek urological evaluation if they experience late recurrent symptoms [588].

11.6 Risk-stratified proposals during follow-up after urethral surgery

Cost of follow-up after urethroplasty is higher in the first year after the procedure [589]. In a literature review it ranged between 205 to 1,784 US Dollars, with higher costs associated to posterior urethral repairs [589]. As the risk of recurrence and side effects are related to the type of stricture and urethroplasty, a different follow-up schedule was proposed and shown to be cost-effective in the USA, potentially saving up to 85% of costs after five years [561]:

- Urethroplasties with a low risk of recurrence (EPA urethroplasty without history of radiotherapy, hypospadias, or LS features) could be safely followed up based on monitoring of symptoms, using selfadministered IPSS questionnaire, every three months for one year, and annually thereafter.
- Urethroplasties with standard risk of recurrence (urethroplasty using grafts, flaps, and/or post-irradiation, hypospadias and/or LS patients) could combine IPSS questionnaire + flowmetry every three months for one year, and annually thereafter. Additionally, RUG at three and twelve months should be performed.

In this protocol, urethrocystoscopy is only performed if required [561]. Another suggested follow-up protocol includes urethrocystoscopy or RUG/VCUG at three months post-operatively, in order to rule out early failures, especially in case of graft use. If there is evidence of good anatomical outcome in these tests, flowmetry and questionnaire results at three months should be considered as the new baseline. Thereafter, follow-up could be safely and routinely performed with non-invasive tests (flowmetry – evaluating Q_{max} and the shape of curve – and questionnaires). Any deterioration should be further investigated with a urethrocystoscopy [577].

A recently suggested protocol also included assessment of LUTS, sexual function (erectile and ejaculatory), and LUT pain, that need to be compared with pre-operative findings which should include a PROM questionnaire [560]. Cystoscopy and flowmetry should be performed between three to six months postoperatively, and flowmetry findings should be considered as the new baseline for longitudinal follow-up. Future significant decline (25-30%) in Q_{max} or Q_{max} - (average flow rate) should trigger new cystoscopy to rule out anatomic recurrence, even in patients who are symptom-free [560]. A routine cystoscopy at twelve to fifteen months should be performed at the surgeon's discretion, based on risk assessment of three aspects: higher-risk patients, evidence of partial urethral narrowing at three-month assessment, low-volume surgeons [560].

Summary of evidence	LE
The higher percentage of recurrences presents during the first twelve months, after urethroplasty surgery.	2a
Risk-adjusted follow-up protocols are cost-effective and safe for the patients.	3

Recommendations	Strength rating
Offer a routine follow-up of at least one year after urethroplasty.	Strong
Adopt a risk-adjusted follow-up protocol.	Weak

11.7 Follow-up protocol proposal after urethroplasty

11.7.1 ***Surgeries with low risk of recurrence***

- Anastomotic urethroplasties in the bulbar/(bulbo)membranous segment with no history of radiotherapy, hypospadias, or balanitis xerotica obliterans (BXO)/LS features.

Table 11.3: Follow-up protocol for urethroplasty with low risk of recurrence

Surgery	3 months	12 months	24 months*
Uroflowmetry	+	+	+
PROM (incl. sexual function)	+	+	+
Anatomic evaluation: (Urethrocystoscopy/ RUG-VCUG)	+**	On indication	On indication

**Follow-up could be discontinued after two years, advising the patient to seek urological evaluation if symptoms worsen. Academic centres could increase the length of follow-up for research purposes.*
***The Panel suggests performing an anatomic assessment at three months.*

11.7.2 ***Surgical management options with standard risk of recurrence***

- Anastomotic urethroplasties in the bulbar segment with prior history of radiotherapy, hypospadias, or BXO/ LS features;
- Penile urethroplasties;
- Non-traumatic posterior urethroplasties;
- Graft or/and flap – substitution – urethroplasties.

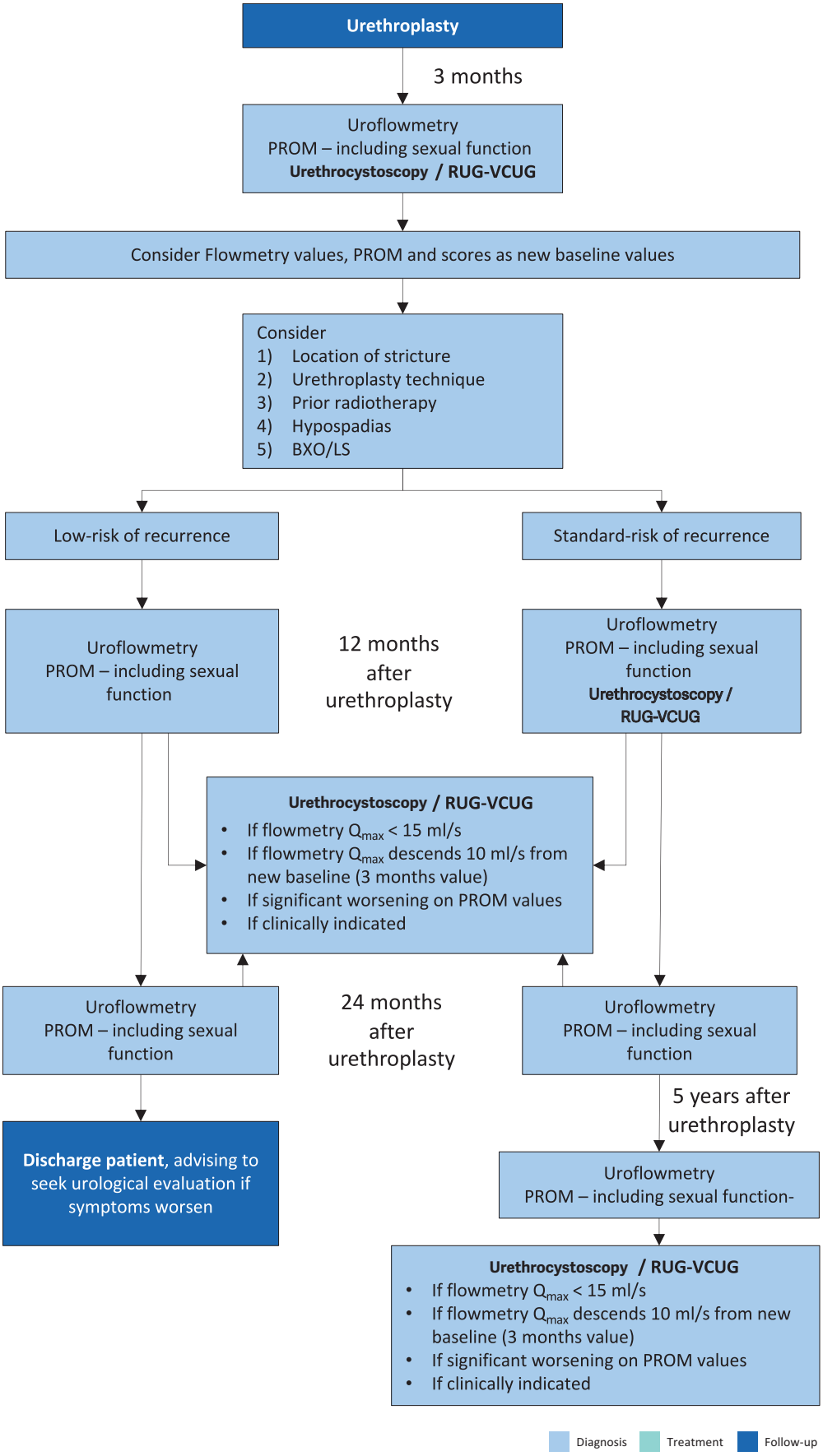
Table 11.4: Follow-up protocol for urethroplasty with standard risk of recurrence

Surgery	3 months	12 months	24 months	5 years *
Uroflowmetry	+	+	+	+
PROM (incl. sexual function)	+	+	+	+
Anatomic evaluation: (Urethrocystoscopy/ RUG-VCUG)	+	+	+	On indication

** Follow-up could be discontinued after five years, advising the patient to seek urological evaluation if symptoms worsen. A longer follow-up period should be considered after penile and substitution urethroplasties. Academic centres could increase the length of follow-up for research purposes.*

Please see Figure 11.1 for further guidance.

Figure 11.1: Follow-up after urethroplasty



BXO = balanitis xerotica obliterans; LS = lichen sclerosus; PROM = patient reported outcome measure; Q_{max} = maximum flow rate; RUG = retrograde urethrography; VCUG = voiding cystourethrography.

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13. CONFLICT OF INTEREST

All members of the Urethral Strictures Guidelines Panel have provided disclosure statements of all relationships that they have that might be perceived as a potential source of a conflict of interest. This information is publicly accessible through the European Association of Urology website: http://www.uroweb.org/guidelines/.
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.

14. CITATION INFORMATION

The format in which to cite the EAU Guidelines will vary depending on the style guide of the journal in which the citation appears. Accordingly, the number of authors or whether, for instance, to include the publisher, location, or an ISBN number may vary.

The compilation of the complete Guidelines should be referenced as:
EAU Guidelines. Edn. presented at the EAU Annual Congress Paris 2024. ISBN 978-94-92671-23-3.

If a publisher and/or location is required, include:
EAU Guidelines Office, Arnhem, the Netherlands. http://uroweb.org/guidelines/compilations-of-all-guidelines/

References to individual guidelines should be structured in the following way:
Contributors' names. Title of resource. Publication type. ISBN. Publisher and publisher location, year.

EAU Guidelines on

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1. INTRODUCTION

1.1 Aim and objectives

This overview represents the updated European Association of Urology (EAU) Guidelines for Urological Infections. The aim is to provide practical recommendations on the prevention and treatment of urinary tract infections (UTIs) and male accessory gland infections. These guidelines also aim to address the important public health aspects of infection control and antimicrobial stewardship. Separate EAU guidelines 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, 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 references/individual circumstances of patients into account. Guidelines are not mandates and do not purport to be a legal standard of care.

1.2 Panel composition

The EAU Guidelines Panel on Urological Infections consists of an international multi-disciplinary group of urologists, with particular expertise in this area, an infectious disease specialist and a clinical microbiologist. 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, the Pocket Guidelines, is available in print. This is an abridged version, 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 2024 document presents a limited update of the 2023 publication.

1.4.1 Summary of changes

Key changes in the 2024 guideline:-

- Section 3.3 - Asymptomatic Bacteriuria in Adults – This section has been extensively updated resulting in a new recommendation and a revised recommendation.

Recommendations	Strength rating
Do not screen or treat asymptomatic bacteriuria in patients prior to cardiovascular surgeries.	Weak
Screen for and treat asymptomatic bacteriuria in pregnant women with standard short course treatment or single dose fosfomycin trometamol.	Weak

- Section 3.16.2.8 – Peri-Procedural Antibiotic Prophylaxis - Prostate Biopsy – The text of this section has been updated, following assessment of the literature.

2. METHODS

2.1 Introduction

For the 2024 Urological Infections Guidelines, new and relevant evidence was identified, collated and appraised through a structured assessment of the literature for sections 3.3 Asymptomatic Bacteriuria in Adults and 3.16.2.8 Peri-Procedural Antibiotic Prophylaxis - Prostate Biopsy. Broad and comprehensive literature searches, covering these sections were performed. Databases searched included Medline, EMBASE, and the Cochrane Libraries. The time frames covered and the number of unique records identified, retrieved and screened for relevance for each section were:

Section	No. of unique records	Search time frame
3.3 Asymptomatic Bacteriuria in Adults	1,503	Dec 1st 2016 - June 1st 2023
3.16.2.8 Peri-Procedural Antibiotic Prophylaxis - Prostate Biopsy	179	June 1st 2022 - June 1st 2023

Detailed search strategies are available online: https://uroweb.org/guidelines/urological-infections/publications-appendices. In addition, the current evidence base of section 3.5 Recurrent UTI was re-assessed and the recommendations reviewed.

Recommendations within the Guidelines are developed by the panels to prioritise clinically important care decisions. The strength of each recommendation is determined by the balance between desirable and undesirable consequences of alternative management strategies, the quality of the evidence (including certainty of estimates), and the nature and variability of patient values and preferences. This decision process, which can be reviewed in the strength rating forms which accompany each guideline statement, addresses a number of key elements:

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

Strong recommendations typically indicate a high degree of evidence quality and/or a favourable balance of benefit to harm and patient preference. Weak recommendations typically indicate availability of lower quality evidence, and/or equivocal balance between benefit and harm, and uncertainty or variability of patient preference [4].

Additional methodology information and a list of associations endorsing the EAU Guidelines can be found in the online: https://uroweb.org/eau-guidelines/methodology-policies.

2.2 Review

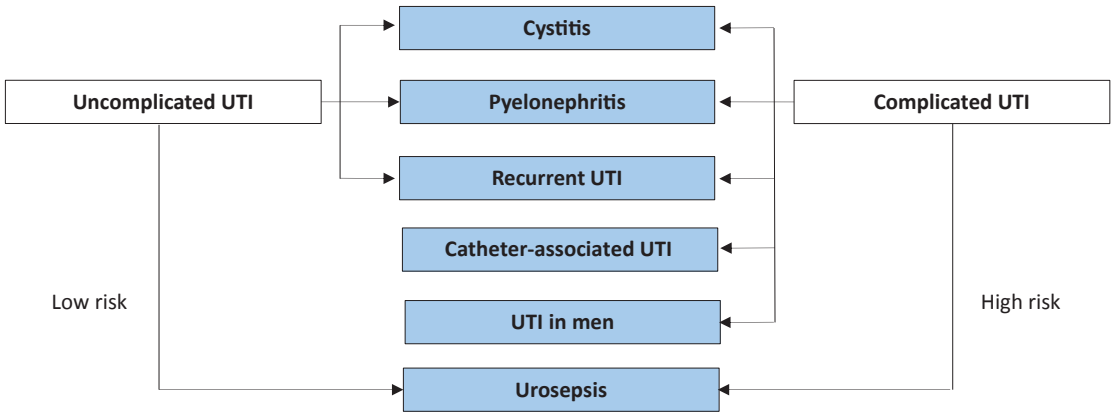
This document was subject to independent peer review prior to publication in 2019.

3. THE GUIDELINE

3.1 Classification

Different classification systems of UTI exist. Most widely used are those developed by the Centres for Disease Control and Prevention (CDC) [5], Infectious Diseases Society of America (IDSA) [6], European Society of Clinical Microbiology and Infectious Diseases (ESCMID) [7] as well as the U.S. Food and Drug Administration (FDA) [8, 9]. Current UTI guidelines frequently use the concept of uncomplicated and complicated UTI with a number of modifications (Figure 1). In 2011 the EAU Section of Infections in Urology proposed the ORENUC classification system based on the clinical presentation of the UTI, the anatomical level of the UTI, the grade of severity of the infection, the categorisation of risk factors and availability of appropriate antimicrobial therapy [10].

Figure 1: Concept of uncomplicated and complicated UTI



The following classification of UTIs is adopted in the EAU Urological Infections Guidelines:

Classification of UTI	
Uncomplicated UTIs	Acute, sporadic or recurrent lower (uncomplicated cystitis) and/or upper (uncomplicated pyelonephritis) UTI, limited to non-pregnant women with no known relevant anatomical and functional abnormalities within the urinary tract or comorbidities.
Complicated UTIs	All UTIs which are not defined as uncomplicated. Meaning in a narrower sense UTIs in a patient with an increased chance of a complicated course: i.e. all men, pregnant women, patients with relevant anatomical or functional abnormalities of the urinary tract, indwelling urinary catheters, renal diseases, and/or with other concomitant immunocompromising diseases for example, diabetes.
Recurrent UTIs	Recurrences of uncomplicated and/or complicated UTIs, with a frequency of at least three UTIs/year or two UTIs in the last six months.
Catheter-associated UTIs	Catheter-associated urinary tract infection (CA-UTI) refers to UTIs occurring in a person whose urinary tract is currently catheterised or has had a catheter in place within the past 48 hours.
Urosepsis	Urosepsis is defined as life threatening organ dysfunction caused by a dysregulated host response to infection originating from the urinary tract and/or male genital organs [11].

3.2 Antimicrobial Stewardship

Although the benefits to patients of antibiotic use are clear, overuse and misuse have contributed to the growing problem of resistance amongst uropathogenic bacteria, which is a serious threat to public health [12, 13]. In acute care hospitals, 20-50% of prescribed antibiotics are either unnecessary or inappropriate [14]. In response, a worldwide initiative seeks to incorporate Antimicrobial Stewardship programs in healthcare [15]. Antimicrobial Stewardship aims to optimise clinical outcomes and ensure cost-effective therapy whilst minimising unintended consequences of antimicrobial use such as healthcare associated infections including *Clostridioides difficile,* toxicity, selection of virulent organisms and emergence of resistant bacterial strains [16].

Stewardship programs have two main sets of actions. The first set mandates use of recommended care at the patient level conforming to guidelines. The second set describes strategies to achieve adherence to the mandated guidance. These include persuasive actions such as education and feedback together with restricting availability linked to local formularies. A Cochrane Review of effectiveness of interventions to improve antibiotic prescribing practices for hospital inpatients, updated in 2017, found high-certainty evidence that such interventions are effective in increasing adherence with antibiotic policy leading to reduced antibiotic treatment duration and that it may also reduce hospital stay. The review found no evidence that reduced antibiotic usage increased mortality [17].

The important components of antimicrobial stewardship programs are [18]:

- 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 and clinical microbiologists;
- audit of adherence and treatment outcomes;
- regular monitoring and feedback to prescribers of their performance and local pathogen resistance profiles.

A 2016 systematic review of evidence for effectiveness of various Antimicrobial Stewardship interventions in healthcare institutions identified 145 studies of nine Stewardship objectives. Guideline-driven empirical therapy using a restricted choice of antibiotics and including de-escalation, intravenous to oral switch, therapeutic drug monitoring, and bedside consultation resulted in a 35% (95% CI 20-46%) relative risk reduction (RRR) in mortality. Use of de-escalation (tailoring to a more narrow spectrum agent), showed a RRR of 56% (95% CI 34 – 70%) for mortality [19].

To facilitate local initiatives and audit, a set of valid, reliable, and applicable indicators of the quality of antibiotic use in the treatment of hospitalised patients with complicated UTI was developed [20]. Its use in the Netherlands appeared to result in shortened hospital stay [21]. A literature search of Pubmed from April 2014 [19], to February 2017 identified no further randomised controlled trials (RCTs) relating to stewardship programmes for UTIs. Studies to provide high-quality evidence of effectiveness of Stewardship programmes in urology patients are urgently needed.

3.3 Asymptomatic bacteriuria in adults

*3.3.1 **Background***

Urinary growth of bacteria in an asymptomatic individual (asymptomatic bacteriuria - ABU) is common, and corresponds to a commensal colonisation [22]. Clinical studies have shown that ABU may protect against superinfecting UTI, thus treatment of ABU should be performed only in cases of proven benefit for the patient to avoid the risk of selecting antimicrobial resistance and eradicating a potentially protective ABU strain [23, 24]. The aim of this section is to support the clinician in deciding when ABU should or should not be treated.

*3.3.2 **Epidemiology, aetiology and pathophysiology***

Asymptomatic bacteriuria occurs in an estimated 1-5% of healthy pre-menopausal females. Increasing to 4-19% in otherwise healthy elderly females and men, 0.7-27% in patients with diabetes, 2-10% in pregnant women, 15-50% in institutionalised elderly populations, and in 23-89% in patients with spinal cord injuries [25]. Asymptomatic bacteriuria in younger men is uncommon, but when detected, chronic bacterial prostatitis must be considered. The spectrum of bacteria in ABU is similar to species found in uncomplicated or complicated UTIs, depending on the presence of risk factors (see sections 3.4 and 3.7).

*3.3.3 **Diagnostic evaluation***

Asymptomatic bacteriuria is defined by a mid-stream sample of urine showing bacterial growth ≥ 10^5 cfu/mL in two consecutive samples in women [26] and in one single sample in men [27] in an individual without urinary tract symptoms. Cystoscopy and/or imaging of the upper urinary tract is not mandatory if the medical history is otherwise without remark. If persistent growth of urease producing bacteria, i.e. *Proteus mirabilis* is detected, stone formation in the urinary tract must be excluded [28, 29, 235]. In men, a digital rectal examination (DRE) has to be performed to investigate the possibility of prostate diseases (see section 3.11).

*3.3.4 **Evidence summary***

A systematic search of the literature from November 2016 to January 2000 identified 3,582 titles of which 224 were selected for full text review and 50 were included [30]. For the subgroups of pregnancy, prior to urologic surgeries, post-menopausal women and institutionalised elderly patients only data from RCTs were included, on which a meta-analysis was performed [30]. For the other subgroups non-RCTs were also included in the narrative analysis [30]. An update systematic literature search from 1st December 2016 to 1st June 2023 identified 1,503 titles of which 36 were selected for full text review and 18 were included. The following patient populations were not covered by the systematic review: immuno-compromised patients; and patients with indwelling catheters. For these groups the guideline was updated using a structured PubMed search. The evidence question addressed was: What is the most effective management for people with asymptomatic bacteriuria?

*3.3.5 **Disease management***

3.3.5.1 Patients without identified risk factors

Asymptomatic bacteriuria does not cause renal disease or damage [31]. Only one prospective, non-randomised study investigated the effect of treatment of ABU in adult, non-diabetic, non-pregnant women [32], and found no difference in the rate of symptomatic UTIs. Furthermore, as the treatment of ABU has been proven to be unnecessary in most high-risk patient subgroups, there is panel consensus that the results of these subgroups can also be applied to patients without identified risk factors. Therefore, screening and treatment of ABU is not recommended in patients without risk factors.

3.3.5.2 Patients with ABU and recurrent UTI, otherwise healthy

One RCT investigated the effect of ABU treatment in female patients with recurrent symptomatic UTI without identified risk factors [24] and demonstrated that treatment of ABU increases the risk for a subsequent symptomatic UTI episode, compared to non-treated patients (RR 0.28, 95% CI 0.21 to 0.38; n=673). This protective effect of spontaneously developed ABU can be used as part of prevention in female patients with recurrent symptomatic UTI; therefore, treatment of ABU is not recommended.

3.3.5.3 Pregnant women

3.3.5.3.1 Is treatment of ABU beneficial in pregnant women?

Twelve RCTs comparing antibiotic treatments of ABU with placebo controls or no treatment [33-44], with different antibiotic doses and regimens were identified, ten published before 1988 and one in 2015. Eleven RCTs (n=2,002) reported on the rate of symptomatic UTIs [33, 35-43, 45]. Antibiotic treatment significantly reduced the number of symptomatic UTIs compared to placebo or no treatment (average RR 0.22, 95% CI 0.12 to 0.40).

Six RCTs reported on the resolution of bacteriuria [33-35, 37, 40, 42]. Antibiotic treatment was effective in the resolution of bacteriuria compared to placebo (average RR 2.99, 95% CI 1.65 to 5.39; n=716). Eight RCTs reported on the rate of low birthweights [33, 35-38, 41, 44, 45]. Antibiotic treatment was associated with lower rates of low birthweight compared to placebo or no treatment (average RR 0.58, 95% CI 0.36 to 0.94; n=1689). Four RCTs reported on the rate of preterm deliveries [41, 42, 44, 45]. Antibiotic treatment was associated with lower rates of preterm delivery compared to placebo or no treatment (average RR 0.34, 95% CI 0.18 to 0.66; n=854). Three additional systematic reviews and meta-analyses have reported that treatment of ABU in pregnancy may be associated with a decreased rate of pyelonephritis, low birthweight or preterm delivery [46-48]. However, they also emphasised the low to very low quality of the evidence of the identified studies.

Based on the beneficial maternal and foetal effects of antibiotic treatment pregnant women should be screened and treated for ABU. However, the panel would like to emphasise that most available studies have low methodological quality and are from the 60s to 80s. Diagnostic and treatment protocols and accessibility to medical services have dramatically changed since then; therefore, the quality of evidence for this recommendation is low. In a newer study of higher methodological quality the beneficial effects of antibiotic treatment are not as evident [45]. Therefore, it is advisable to consult national recommendations for pregnant women.

3.3.5.3.2 Which treatment duration should be applied to treat ABU in pregnancy?

Sixteen RCTs comparing the efficacy of different antibiotic treatments in pregnant women with ABU were identified [49-64]. There was significant heterogeneity amongst the studies. Studies compared different antibiotic regimens or the same antibiotic regimens with different durations. The duration of treatment ranged from single dose to continuous treatment (until delivery). For practical purposes the grouping strategy used by the previously published Cochrane Review by Widmer *et al.* was adopted with some modifications [65]. The following treatment groups were used for comparison:

1. single dose (single day);
2. short course (2-7 days);
3. long course (8-14 days);
4. continuous (until delivery).

Nine studies compared single dose to short course treatment [50, 54, 55, 59-64], one study compared single dose to long course treatment [58] and one study compared long course to continuous treatment [51]. As long term and continuous antibiotic treatment is not used in current practice, only studies comparing single dose to standard short course treatment are presented.

3.3.5.3.2.1 Single dose vs. short course treatment

Three RCTs reported on the rate of symptomatic UTIs [54, 63, 64], with no significant difference between the two durations (average RR 1.07, 95% CI 0.47 to 2.47; n=891). Nine RCTs reported on the rate of ABU resolution [50, 54, 55, 59-64], with no significant difference between the two durations (average RR 0.97, 95% CI 0.89 to 1.07; n=1,268). Six RCTs reported on the rate of side effects [50, 54, 59, 60, 62, 63]. Single dose treatment was associated with significantly less side effects compared to short course treatment (average RR 0.40, 95% CI 0.22 to 0.72; n=458). Three RCTs reported on the rate of preterm deliveries [54, 56, 64], with no significant difference between the two durations (average RR 1.16, 95% CI 0.75 to 1.78; n=814). One RCT reported on the rate of low birthweights [64]. There were significantly more babies with low birthweight in the single dose duration compared to short course treatment (average RR 1.65, 95% CI 1.06 to 2.57; n=714).

According to the data analysis, single dose treatment was associated with a significantly lower rate of side effects but a significantly higher rate of low birthweight. A meta-analysis on the use of single dose fosfomycin trometamol in women with lower uncomplicated UTIs or ABU reported on a subgroup analysis of pregnant women with ABU [66]. The study identified five RCTs involving 577 patients. The resolution rate of ABU in pregnant women treated with single dose fosfomycin trometamol was not significantly different from those who received other antibiotics (OR 1.32, 95% CI 0.78–2.22, p=0.30). Therefore, standard short course treatment or single dose fosfomycin trometamol should be applied to treat ABU in pregnancy; however, it should be emphasised that the overall quality of the scientific evidence backing this recommendation is low.

3.3.5.4 Patients with identified risk-factors

3.3.5.4.1 Diabetes mellitus

Diabetes mellitus, even when well regulated, is reported to correlate to a higher frequency of ABU [67]. One RCT demonstrated that eradicating ABU did not reduce the risk of symptomatic UTI and infectious complications in patients with diabetes mellitus. The time to first symptomatic episode was also similar in both groups. Furthermore, untreated ABU did not correlate to diabetic nephropathy [68]. Screening and treatment of ABU in well-controlled diabetes mellitus is therefore not recommended. However, poorly regulated diabetes is a risk factor for symptomatic UTI and infectious complications.

3.3.5.4.2 ABU in post-menopausal women

Elderly women have an increased incidence of ABU [69]. Four RCTs compared antibiotic treatment of ABU with placebo controls or no treatment, in a post-menopausal female population, with different antibiotic doses and regimens [70-73]. Women in these studies were mostly nursing home residents, which may bias the results of this analysis. Three RCTs reported on the rate of symptomatic UTIs (average RR 0.71, 95% CI 0.49 to 1.05; 208 women) and the resolution of bacteriuria (average RR 1.28, 95% CI 0.50 to 3.24; 203 women) [54, 63, 64], with no significant benefit of antibiotic treatment. Therefore, ABU in post-menopausal women does not require treatment, and should be managed as for pre-menopausal women.

3.3.5.4.3 Elderly institutionalised patients

The rate of ABU is 15-50% in elderly institutionalised patients [74]. Differential diagnosis of ABU from symptomatic UTI is difficult in the multi-diseased and mentally deteriorated patients, and is probably a cause of unnecessary antibiotic treatment [75, 76]. Seven RCTs compared antibiotic treatment of ABU with placebo controls or no treatment in elderly patients, with different antibiotic doses and regimens [70-73, 77-79].

Three RCTs reported on the rate of symptomatic UTIs [70, 72, 77]. Antibiotic treatment was not significantly beneficial in reducing the rate of symptomatic UTIs compared to placebo or no treatment (average RR 0.68, 95% CI 0.46 to 1.00; n=210). Six RCTs reported on the resolution of bacteriuria [70, 72, 73, 77-79]. There was no benefit of antibiotic treatment compared to placebo in the resolution of ABU (average RR 1.33, 95% CI 0.63 to 2.79; n=328). One RCT compared the rates of incontinence in this patient group before and after the eradication of ABU and found no effect of antibiotic treatment [80]. A subsequent systematic review and meta-analysis of nine RCTs found that antibiotic treatment of ABU in this group was associated with significantly more adverse effects with no clinical benefit [81]. Therefore, screening and treatment of ABU is not recommended in this patient group.

3.3.5.4.4 Patients with renal transplants

Two RCTs and two retrospective studies compared the effect of antibiotic treatment to no treatment in renal transplant patients [82-85]. Meta-analysis of the two RCTs did not find antibiotic treatment beneficial in terms of reducing symptomatic UTIs between 12 and 22 months after renal transplantation (RR 0.86, 95% CI 0.51 to 1.45; n=200). The two retrospective studies reached the same conclusion. Furthermore, there were no significant differences in the rate of ABU clearance, graft loss or change in renal function during long-term follow-up to 24 months [82-85].

A further two RCTs [86, 87], one observational study [88] and two systematic reviews and meta-analyses [89, 90] were identified. The first RCT reported that during the first 2 months following renal transplantation the incidence of and risk for UTIs (25% vs. 10%, HR 2.8, 95% CI 0.8-9.1, p=0.07) and pyelonephritis (15% vs. 2.5%, HR 6.5, 95% CI 0.8-54.7, p=0.08) was higher in patients receiving antibiotic treatment for ABU vs. no treatment [86]. In the second RCT no difference in acute graft pyelonephritis was found between the treatment and no treatment group (12.2% vs 8.7%, RR 1.40, 95% CI 0.40-4.87) in the first year after renal transplantation; however, rates of antimicrobial resistance were higher in the treatment group [87]. The first of the two additional meta-analyses reported the same results as the original study [89]. The second meta-analysis of n=1,353 patients reported ABU incidence rates of 22% in the first month and 32% during the first year after renal transplantation [90]. The analysis did not find a correlation between ABU and acute graft pyelonephritis (OR 1.8, 95% CI 0.78-1.79), a benefit of ABU antibiotic treatment on the risk of UTI (OR 1.08, 95% CI 0.63-1.84) or a change of renal function (mean difference in serum creatinine concentration - 0.03 mg/dL [95% CI 0.15-0.10]) [90].

Therefore, treatment of ABU is not recommended in renal transplant recipients.

3.3.5.4.5 Patients with dysfunctional and/or reconstructed lower urinary tracts

Patients with lower urinary tract dysfunction (LUTD) (e.g., neurogenic lower urinary tract dysfunction (NLUTD) secondary to multiple sclerosis, spinal cord injury patients, patients with incomplete bladder emptying, patients using clean intermittent catheterisation [CIC], or patients with reconstructed lower urinary tract including ileal conduits, orthotopic bladder replacement or continent reservoirs frequently become colonised [91, 92]. A systematic review reported ABU prevalence rates ranging from 25-86% for intestinal conduits in 4 studies and 9.1-85% for orthotopic neobladders in 9 studies [93]. Studies have shown no long-term benefit in ABU treatment in these patient groups [84, 85, 93].

Furthermore, in LUTD patients who do not spontaneously develop ABU, deliberate colonisation with an ABU strain (*Escherichia coli* 83972) has shown a protective effect against symptomatic recurrences [94, 95]. Screening and treatment of ABU in these patient groups is therefore, not recommended. If these patient groups develop recurrent symptomatic UTI (see section 3.5) the potential protective effect of a spontaneously developed ABU against UTI must be considered before any treatment.

3.3.5.4.6 Patients with catheters in the urinary tract

Patients with indwelling or suprapubic catheters and nephrostomy tubes invariably become carriers of ABU, with antibiotic treatment showing no benefit [96]. This is also applicable for patients with ABU and indwelling ureteral stents [97]. Routine treatment of catheter-associated bacteriuria is not recommended. For detailed recommendations see section 3.8.

3.3.5.4.7 Patients with ABU subjected to catheter placements/exchanges

In patients subjected to uncomplicated placement/exchanges of indwelling urethral catheters ABU is not considered a risk factor and should not be screened or treated [98]. In patients subjected to placement/exchanges of nephrostomy tubes and indwelling ureteral stents, ABU is considered a risk factor for infectious complications [99].

3.3.5.4.8 Immuno-compromised and severely diseased patients, patients with candiduria

These patient groups have to be considered individually and the benefit of screening and treatment of ABU should be reviewed in each case. Patients with asymptomatic candiduria may, although not necessarily, have an underlying disorder or defect. Treatment of asymptomatic candiduria is not recommended [100].

3.3.5.5 Prior to urological surgery

In diagnostic and therapeutic procedures not entering the urinary tract, ABU is generally not considered as a risk factor, and screening and treatment are not considered necessary. On the other hand, in procedures entering the urinary tract and breaching the mucosa, particularly in endoscopic urological surgery, bacteriuria is a definite risk factor.

Two RCTs [101, 102] and two prospective non-randomised studies [103, 104] compared the effect of antibiotic treatment to no treatment before transurethral prostate or bladder tumour resections. Antibiotic treatment significantly reduced the number of post-operative symptomatic UTIs compared to no treatment in the meta-analysis of the two RCTs (average RR 0.20, 95% CI 0.05 to 0.86; n=167). The rates of post-operative fever and septicaemia were also significantly lower in case of antibiotic treatment compared to no treatment in the two RCTs. One RCT including patients with spinal cord injury undergoing elective endoscopic urological surgeries found no significant difference in the rate of post-operative UTIs between single-dose or 3-5 days short term pre-operative antibiotic treatment of ABU [105].

A urine culture must therefore be taken prior to such interventions and in case of ABU, pre-operative treatment is recommended.

3.3.5.6 Prior to orthopaedic surgery

One RCT (n=471) and one multicentre cohort study (n=303) comparing the treatment of ABU with no treatment prior to orthopaedic surgery (hip arthroplasty/hemiarthroplasty or total knee arthroplasty) were identified [106, 107]. Neither of the studies showed a beneficial effect of antibiotic treatment in terms of prosthetic joint infection (3.8% vs. 0% and 3.9% vs. 4.7%, respectively). The cohort study reported no significant difference in the rate of post-operative symptomatic UTI (0.65% vs. 2.7%) [107]. One further RCT investigated the efficacy of pre-operative ABU treatment with fosfomycin-trometamol for prevention of early-periprosthetic joint infections (PJI) after hip hemiarthroplasty for fractures. Asymptomatic bacteriuria was not predictive of early-PJI (OR: 1.06, 95% CI 0.33 - 3.38), and its treatment did not modify early-PJI incidence (OR: 1.03, 95% CI 0.15 - 7.10) [108]. Furthermore, four additional meta-analyses did not find a benefit for pre-operative screening or treatment of ABU prior to orthopaedic surgery [109-112]. Therefore, treatment of bacteriuria is not recommended prior to arthroplasty surgery.

3.3.5.7 Prior to cardiovascular surgery

One systematic review and meta-analysis including three retrospective non-randomised studies involving a total of 1,116 patients was identified [113]. The procedures performed were non-valvular coronary artery bypass grafting (42%), valvular replacements (51%) and thoracic aortic surgeries (7%). Pre-operative treatment of ABU in 116 patients did not result in significant benefit regarding the rate of SSI compared to no treatment (12.9% vs. 8.2%, p=.0.086). A moderate heterogeneity was observed in the meta-analysis and pre-operative treatment of ABU had no significant effect on the rate of infectious complications (OR: 1.38, 95% CI 0.56 - 3.39). Due to the very low number, retrospective and non-randomised design of the included studies limited conclusions can be drawn from this. Further studies with appropriate design and sample size are needed to confirm these findings.

3.3.5.8 Pharmacological management

If the decision is taken to eradicate ABU, the same choice of antibiotics and treatment duration as in symptomatic uncomplicated (section 3.4.4.4) or complicated (section 3.7.5) UTI can be given, depending on gender, medical background and presence of complicating factors. Treatment should be tailored and not empirical.

3.3.6 ***Follow-up***

There are no studies focusing on follow-up after treatment of ABU.

3.3.7 ***Summary of evidence and recommendations for the management of ABU***

Summary of evidence	**LE**
Treatment of asymptomatic bacteriuria is not beneficial in the following conditions: • women without risk factors; • patients with well-regulated diabetes mellitus; • post-menopausal women; • elderly institutionalised patients; • patients with dysfunctional and/or reconstructed lower urinary tracts; • patients with renal transplants; • patients prior to arthroplasty surgeries; • patients prior to cardiovascular surgeries.	 3b 1b 1a 1a 2b 1a 1a 1b
Treatment of asymptomatic bacteriuria is harmful in patients with recurrent urinary tract infections.	1b
Treatment of asymptomatic bacteriuria is beneficial prior to urological procedures breaching the mucosa.	1a
Treatment of asymptomatic bacteriuria in pregnant women was found to be beneficial by meta-analysis of the available evidence; however, most studies are old. A recent study reported lower rates of pyelonephritis in low-risk women.	1a

Recommendations	Strength rating
Do not screen or treat asymptomatic bacteriuria in the following conditions: • women without risk factors; • patients with well-regulated diabetes mellitus; • post-menopausal women; • elderly institutionalised patients; • patients with dysfunctional and/or reconstructed lower urinary tracts; • patients with renal transplants; • patients prior to arthroplasty surgeries; • patients with recurrent urinary tract infections.	Strong
Do not screen or treat asymptomatic bacteriuria in patients prior to cardiovascular surgeries.	Weak
Screen for and treat asymptomatic bacteriuria prior to urological procedures breaching the mucosa.	Strong
Screen for and treat asymptomatic bacteriuria in pregnant women with standard short course treatment or single dose fosfomycin trometamol.	Weak

3.4 Uncomplicated cystitis

*3.4.1 **Introduction***

Uncomplicated cystitis is defined as acute, sporadic or recurrent cystitis limited to non-pregnant women with no known relevant anatomical and functional abnormalities within the urinary tract or comorbidities.

*3.4.2 **Epidemiology, aetiology and pathophysiology***

Almost half of all women will experience at least one episode of cystitis during their lifetime. Nearly one in three women will have had at least one episode of cystitis by the age of 24 years [114]. Risk factors include sexual intercourse, use of spermicides, a new sexual partner, a mother with a history of UTI and a history of UTI during childhood. The majority of cases of uncomplicated cystitis are caused by *E. coli*.

*3.4.3 **Diagnostic evaluation***

3.4.3.1 Clinical diagnosis

The diagnosis of uncomplicated cystitis can be made with a high probability based on a focused history of lower urinary tract symptoms (dysuria, frequency and urgency) and the absence of vaginal discharge [115, 116]. In elderly women genitourinary symptoms are not necessarily related to cystitis [117, 118].

3.4.3.2 Differential diagnosis

Uncomplicated cystitis should be differentiated from ABU, which is considered not to be infection but rather a commensal colonisation, which should not be treated and therefore not screened for, except if it is considered a risk factor in clearly defined situations (see section 3.3).

3.4.3.3 Laboratory diagnosis

In patients presenting with typical symptoms of an uncomplicated cystitis urine analysis (i.e. urine culture, dip stick testing, etc.) leads only to a minimal increase in diagnostic accuracy [119]. However, if the diagnosis is unclear dipstick analysis can increase the likelihood of an uncomplicated cystitis diagnosis [120, 121]. Taking a urine culture is recommended in patients with atypical symptoms, as well as those who fail to respond to appropriate antimicrobial therapy [122, 123].

3.4.3.4 Summary of evidence and recommendations for the diagnostic evaluation of uncomplicated cystitis

Summary of evidence	LE
An accurate diagnosis of uncomplicated cystitis can be based on a focused history of lower urinary tract symptoms and the absence of vaginal discharge or irritation.	2b

Recommendations	Strength rating
Diagnose uncomplicated cystitis in women who have no other risk factors for complicated urinary tract infections based on: • a focused history of lower urinary tract symptoms (dysuria, frequency and urgency); • the absence of vaginal discharge.	Strong
Use urine dipstick testing for diagnosis of acute uncomplicated cystitis.	Weak
Urine cultures should be done in the following situations: • suspected acute pyelonephritis; • symptoms that do not resolve or recur within four weeks after completion of treatment; • women who present with atypical symptoms; • pregnant women.	Strong

*3.4.4 **Disease management***

Antimicrobial therapy is recommended because clinical success is significantly more likely in women treated with antimicrobials compared with placebo [124]. In female patients with mild to moderate symptoms, symptomatic therapy (e.g. Ibuprofen, phytotherapy), as an alternative to antimicrobial treatment, may be considered in consultation with individual patients [125-129]. The choice of antimicrobial therapy should be guided by [115]:

- spectrum and susceptibility patterns of the aetiological pathogens;
- efficacy for the particular indication in clinical studies;
- tolerability and adverse reactions;
- adverse ecological effects;
- costs;
- availability.

According to these principles and the available susceptibility patterns in Europe, oral treatment with fosfomycin trometamol 3 g single dose, pivmecillinam 400 mg three times a day for three to five days, and nitrofurantoin (e.g. nitrofurantoin monohydrate/macrocrystals 100 mg twice daily for five days), should be considered for first-line treatment, when available [130-133].

Alternative antimicrobials include trimethoprim alone or combined with a sulphonamide. Co-trimoxazole (160/800 mg twice daily for three days) or trimethoprim (200 mg twice daily for five days) should only be considered as drugs of first choice in areas with known resistance rates for *E. coli* of < 20% [134, 135].

Aminopenicillins are no longer suitable for empirical therapy because of worldwide high *E. coli* resistance. Aminopenicillins in combination with a beta-lactamase inhibitor such as ampicillin/sulbactam or amoxicillin/clavulanic acid and oral cephalosporins are not recommended for empirical therapy due to ecological collateral damage, but may be used in selected cases [136, 137].

Important note:
On 11th March 2019, the European Commission implemented stringent regulatory conditions regarding the use of fluoroquinolones due to their disabling and potentially long-lasting side effects [138]. This legally binding decision is applicable in all EU countries. National authorities have been urged to enforce this ruling and to take all appropriate measures to promote the correct use of this class of antibiotics. In uncomplicated cystitis a fluoroquinolone should only be used when it is considered inappropriate to use other antibacterial agents that are commonly recommended for the treatment of these infections [138].

3.4.4.1 Cystitis in pregnancy

Short courses of antimicrobial therapy can also be considered for treatment of cystitis in pregnancy [139], but not all antimicrobials are suitable during pregnancy. In general, penicillins, cephalosporins, fosfomycin, nitrofurantoin (not in case of glucose-6-phosphate dehydrogenase deficiency and during the end of pregnancy), trimethoprim (not in the first trimenon) and sulphonamides (not in the last trimenon), can be considered.

3.4.4.2 Cystitis in men

Cystitis in men without involvement of the prostate is uncommon and should be classed as a complicated infection. Therefore, treatment with antimicrobials penetrating into the prostate tissue is needed in males with symptoms of UTI. A treatment duration of at least seven days is recommended, preferably with trimethoprim-sulphamethoxazole or a fluoroquinolone if in accordance with susceptibility testing (see section 3.4.4.4) [140].

3.4.4.3 Renal insufficiency

In patients with renal insufficiency the choice of antimicrobials may be influenced by decreased renal excretion; however, most antimicrobials, have a wide therapeutic index. No adjustment of dose is necessary until glomerular filtration rate (GFR) is < 20 mL/min, with the exception of antimicrobials with nephrotoxic potential, e.g. aminoglycosides. The combination of loop diuretics (e.g. furosemide) and a cephalosporin is nephrotoxic. Nitrofurantoin is contraindicated in patients with an estimated glomerular filtration rate (eGFR) of less than 30 ml/min/1.73m2 as accumulation of the drug leads to increased side effects as well as reduced urinary tract recovery, with the risk of treatment failure [141].

3.4.4.4 Summary of evidence and recommendations for antimicrobial therapy for uncomplicated cystitis

Summary of evidence	LE
Clinical success for the treatment of uncomplicated cystitis is significantly more likely in women treated with antimicrobials than placebo.	1b
Aminopenicillins are no longer suitable for antimicrobial therapy in uncomplicated cystitis because of negative ecological effects, high resistance rates and their increased selection for extended spectrum beta-lactamase (ESBL)-producing bacteria.	3

Recommendations	Strength rating
Prescribe fosfomycin trometamol, pivmecillinam or nitrofurantoin as first-line treatment for uncomplicated cystitis in women.	Strong
Do not use aminopenicillins or fluoroquinolones to treat uncomplicated cystitis.	Strong

Table 1: Suggested regimens for antimicrobial therapy in uncomplicated cystitis

Antimicrobial	Daily dose	Duration of therapy	Comments
First-line women			
Fosfomycin trometamol	3 g SD	1 day	Recommended only in women with uncomplicated cystitis.
Nitrofurantoin macrocrystal	50-100 mg four times a day	5 days	
Nitrofurantoin monohydrate/ macrocrystals	100 mg b.i.d	5 days	
Nitrofurantoin macrocrystal prolonged release	100 mg b.i.d	5 days	
Pivmecillinam	400 mg t.i.d	3-5 days	
Alternatives			
Cephalosporins (e.g. cefadroxil)	500 mg b.i.d	3 days	Or comparable
If the local resistance pattern for E. coli is < 20%			
Trimethoprim	200 mg b.i.d	5 days	Not in the first trimenon of pregnancy
Trimethoprim-sulfamethoxazole	160/800 mg b.i.d	3 days	Not in the last trimenon of pregnancy
Treatment in men			
Trimethoprim-sulfamethoxazole	160/800 mg b.i.d	7 days	Restricted to men, fluoroquinolones can also be prescribed in accordance with local susceptibility testing.

SD = single dose; b.i.d = twice daily; t.i.d = three times daily.

3.4.5 Follow-up

Routine post-treatment urinalysis or urine cultures in asymptomatic patients are not indicated [25]. In women whose symptoms do not resolve by end of treatment, and in those whose symptoms resolve but recur within two weeks, urine culture and antimicrobial susceptibility testing should be performed [142]. For therapy in this situation, one should assume that the infecting organism is not susceptible to the agent originally used. Retreatment with a seven-day regimen using another agent should be considered [142].

3.5 Recurrent UTIs

3.5.1 Introduction

Recurrent UTIs (rUTIs) are recurrences of uncomplicated and/or complicated UTIs, with a frequency of at least three UTIs/year or two UTIs in the last six months. Although rUTIs include both lower tract infection (cystitis) and upper tract infection (pyelonephritis), repeated pyelonephritis should prompt consideration of a complicated aetiology. Recurrent UTIs negatively impact patient quality of life leading to a reduction in the quality of social and sexual relationships, self-esteem and capacity for work [143].

3.5.2 Diagnostic evaluation

Recurrent UTIs are common. Risk factors are outlined in Table 2. Initial diagnosis of rUTI should be confirmed by urine culture. An extensive routine workup including cystoscopy, imaging, etc. is not routinely recommended as the diagnostic yield is low [144]. However, it should be performed without delay in atypical cases, for example, if renal calculi, outflow obstruction, interstitial cystitis or urothelial cancer is suspected.

Table 2: Age-related associations of rUTI in women [74, 117, 145]

Young and pre-menopausal women	Post-menopausal and elderly women
Sexual intercourse	History of UTI before menopause
Use of spermicide	Urinary incontinence
A new sexual partner	Atrophic vaginitis due to oestrogen deficiency
A mother with a history of UTI	Cystocele
History of UTI during childhood	Increased post-void urine volume
Blood group antigen secretory status	Blood group antigen secretory status
	Urine catheterisation and functional status
	deterioration in elderly institutionalised women

3.5.3 Disease management and follow-up

Prevention of rUTIs includes counselling regarding avoidance of risk factors, non-antimicrobial measures and antimicrobial prophylaxis [142, 146]. These interventions should be attempted in this order. Any urological risk factor must be identified and treated. Significant residual urine should be treated optimally, including by CIC when judged to be appropriate.

3.5.3.1 Evidence Summary

A broad literature with cut-off of 31st May 2021 identified 3,604 abstracts of which 361 were selected for full text review. In total 114 systematic reviews or guidelines based on systematic literature searches and 131 original publications were selected for further analysis. A further 18 relevant publications were identified from the references of the reviewed studies. Selected studies were assigned to one of nine subgroups based on the method of prevention. An updated search with cut-off date of 1st June 2022 identified a further 316 abstracts of which 25 were selected for further analysis. The evidence question addressed was: In women with recurrent symptomatic lower urinary tract infection what interventions reduce the rate of recurrence?

3.5.3.2 Behavioural modifications

Women with rUTI should be counselled on avoidance of risks (e.g., insufficient drinking, habitual and post-coital delayed urination, wiping from front to back after defecation, douching and wearing occlusive underwear) before initiation of long-term prophylactic drug treatment, although there is limited evidence available regarding these approaches [147, 148]. An open-label RCT found that additional fluid intake of 1.5 L a day in premenopausal women with rUTI who were low-volume drinkers (< 1.5 L a day) reduced the number of cystitis episodes and antibiotic usage over a 12-month period [149]

3.5.3.3 Non-antimicrobial prophylaxis

3.5.3.3.1 Hormonal replacement

Based on the results of four meta-analyses topical oestrogen therapy (either as a creme or a pessary) shows a trend towards rUTI prevention [150-153]. All studies reported that application was superior compared to placebo but was inferior compared to antibiotics. Due to its pharmacokinetics vaginal admission has no systematic side effects, however local irritation and minor bleeding can occur. The use of oral oestrogens was not effective for rUTI prophylaxis compared to placebo, furthermore it was associated with an unfavourable systematic side effect profile. A single prospective, non-comparative study of 30 pre-menopausal women with rUTI on oral contraceptives reported a beneficial effect for additional topical oestrogen therapy [154].

3.5.3.3.2 Immunoactive prophylaxis

Several meta-analyses and systematic reviews based on nine RCTs showed that oral immunotherapy with OM-89 is an effective and safe method for the prevention of rUTIs compared to placebo at short-term follow up (< 6 months) [151, 155, 156].

A vaginal suppository containing ten strains of heat-killed uropathogenic bacteria significantly reduced the risk of rUTI compared to placebo in a meta-analysis of three small RCTs [155-157]. The preventive effect was more pronounced with booster treatment.

A systematic review of two retrospective and three prospective cohort studies concluded that MV140 may decrease the number of rUTI episodes and/or increase the probability of patients being UTI free [158]. A placebo controlled RCT of MV140 reported a significant decrease in rUTI episodes in both MV140 groups vs. placebo [159]. At 12 months follow-up 25% of women treated with placebo (95% CI, 15% to 35%) were UTI free compared with 56% (95% CI, 44% to 67%) and 58% (95% CI, 44% to 67%) of women who received three and six months of MV140 treatment, respectively. The median number of UTI episodes per patient was 3.0 (0.5 to 6.0) for the placebo group compared with 0.0 (0.0 to 1.0) in both groups receiving MV140 [159].

A comparative single-centre study of 124 women vaccinated with StroVac compared to 49 women receiving antibiotic prophylaxis with 24-month follow-up concluded that StroVac is an effective non-antibiotic prophylaxis for rUTI [160]. However, this study was not randomised or blinded resulting in a high risk of bias (selection and imprecision).

3.5.3.3.3 Prophylaxis with probiotics (*Lactobacillus* spp.)

Five meta-analyses with differing results and eleven relevant systematic reviews were identified [151, 161-174]. Two meta-analyses reported significant positive effects for rUTI prevention with effective probiotics compared to placebo [165, 167]. The contradictory results of the four meta-analyses are a result of the analysis of different Lactobacillus strains and different administration regimes, treatment durations, and patient populations. Most studies concluded that not all Lactobacillus strains are effective for vaginal flora restoration and rUTI prevention. The highest efficacy was shown with *L. rhamnosus* GR-1, *L. reuteri* B-54, *L. reuteri* RC-14, *L. casei shirota*, and *L. crispatus* CTV-05 [151, 163, 165, 167]. Although meta-analyses including all known Lactobacilli strains did not show a significant treatment benefit [151, 163, 165, 167], sensitivity analysis excluding studies using ineffective strains resulted in a positive treatment effect [165].

Of the eleven systematic reviews, seven concluded that prophylaxis with vaginal probiotics has a beneficial clinical impact for the prevention of rUTI [152, 153, 161, 164, 166, 168-171, 173]. The available data is too minimal or of low quality to allow the panel to make recommendations on the route of admission, optimal dosage, and treatment duration for probiotic prophylaxis.

3.5.3.3.4 Prophylaxis with cranberry

Seven meta-analyses and several systematic reviews were identified [151, 175-180]. A Cochrane systematic review and meta-analysis found that when compared with placebo, water or not treatment, cranberry products did not significantly reduce the occurrence of symptomatic UTI overall or in women with recurrent UTIs [175]. However, six subsequent meta-analyses concluded that consumption of cranberry-containing products may protect against UTIs in certain patient populations [151, 176-180]. The differing outcomes across the meta-analyses can be contributed to the clinical and methodological heterogeneity of the included studies [181]. A RCT of 145 women randomised to high-dose vs. low-dose cranberry proanthocyanidin extract reported no significant reduction in the number of symptomatic UTI episodes between the groups [182]. Although the efficacy of cranberry products remains unclear, the panel consensus is that clinicians may recommend them for rUTI prevention in women who are informed of the weak evidence base due to their favourable benefit to harm ratio. However, there is no clear clinical evidence regarding the appropriate dose and treatment duration.

3.5.3.3.5 Prophylaxis with D-mannose

A meta-analysis including one RCT, one randomised cross-over trial and one prospective cohort study analysed data on 390 patients and found that D-mannose was effective for rUTI prevention compared to placebo with comparable efficacy to antibiotic prophylaxis [183]. Another systematic review, concluded that D-mannose had a significant effect on UTI, but that further studies were needed to confirm these findings [161]. A further systematic review including 695 patients reported that D-Mannose improved quality of life and significantly reduced rUTIs in both catheter and non-catheter users and was effective in reducing the incidence of rUTIs and prolonging UTI-free periods [184]. However, a Cochrane systematic review including 719 patients was unable to determine if D-mannose when compared to no treatment, other supplements or antibiotics significantly reduced the number of rUTI episodes [185]. The overall quality of the evidence was low.

3.5.3.3.6 Endovesical instillation

Endovesical instillations of hyaluronic acid (HA) and chondroitin sulphate (CS) have been used for glycosaminoglycan (GAG) layer replenishment in the treatment of interstitial cystitis, overactive bladder, radiation cystitis, and for prevention of rUTI [186]. A meta-analysis (n=143) based on two RCTs and two non-RCTs found significantly decreased UTI rates per patient/year and significantly longer mean UTI recurrence times for HA and HA-CS therapy compared to control treatment [187]. In addition, subgroup analysis of the two RCTs using HA-CS reported a significantly decreased UTI rate per patient-year, significantly longer mean UTI recurrence time and a significantly better pelvic pain and urgency/frequency (PUF) total score. However, 24-h urinary frequency measured as number of voids in 3 days were not significantly improved after therapy [187].

Another meta-analysis (n=800) including two RCTs and six non-RCTs found that when compared to control treatment HA, with or without CS, was associated with a significantly lower mean UTI rate per patient-year and a significantly longer time to UTI recurrence [188]. Furthermore, HA-CS therapy was associated with significantly greater mean reductions in PUF total and symptom scores and the percentage of patients with UTI recurrence during follow-up was also lower [188].

As randomised controlled studies are available only for HA plus CS, the quality of evidence is higher for the combination than for HA alone.

3.5.3.3.7 Methenamine hippurate

A Cochrane Review from 2012 based on thirteen studies, with high levels of heterogeneity, concluded that methenamine hippurate may be effective for preventing UTI in patients without renal tract abnormalities, particularly when used for short-term prophylaxis [189]. A meta-analysis from 2021 based on six studies found that although studies showed a trend towards a benefit for methenamine hippurate in prevention of rUTIs there was no statistically significant difference between the efficacy of methenamine hippurate and any comparators [190]. A subsequent RCT including 240 women randomised (1 : 1) to receive once-daily low-dose antibiotic prophylaxis or twice-daily methenamine hippurate for twelve months reported that the incident rate of patient-reported symptomatic UTIs decreased to 1.38 episodes per person per year for the methenamine hippurate group vs. 0.89 episodes per person per year for the antibiotic group. The absolute difference was 0.49 confirming that methenamine hippurate was not inferior to antibiotic prophylaxis. The rate of adverse events was similar in both groups and a sustained benefit for both treatment arms was observed at six months follow-up [191, 192].

3.5.3.4 Antimicrobials for preventing rUTI

3.5.3.4.1 Continuous low-dose antimicrobial prophylaxis and post-coital prophylaxis

Four meta-analyses and numerous systematic reviews and guidelines were identified [153, 193-203]. All available meta-analyses conclude that antibiotic prophylaxis is the most effective approach against UTI recurrences compared with placebo or no treatment [193-195]. Antimicrobials may be given as continuous low-dose prophylaxis for longer periods, or as post-coital prophylaxis. There is no significant difference in the efficacy of the two approaches. There is no consensus about the optimal duration of continuous antimicrobial prophylaxis, with studies reporting treatment duration of three to twelve months. After discontinuation of the drug, UTIs tend to re-occur, especially among those, who have had three or more infections annually. It is mandatory to offer both continuous low-dose antimicrobial and post-coital prophylaxis after counselling, and when behavioural modifications as well as non-antimicrobial measures have been unsuccessful.

Differences in outcomes between antibiotics did not reach statistical significance. The choice of agent should be based on the local resistance patterns. Regimens include nitrofurantoin 50 mg or 100 mg once daily, fosfomycin trometamol 3 g every ten days, trimethoprim 100 mg once daily and during pregnancy cephalexin 125 mg or 250 mg or cefaclor 250 mg once daily [142, 204]. Post-coital prophylaxis should be considered in pregnant women with a history of frequent UTIs before onset of pregnancy, to reduce their risk of UTI [205].

3.5.3.4.2 Self-diagnosis and self-treatment

In patients with good compliance, self-diagnosis and self-treatment with a short course regimen of an antimicrobial agent should be considered [206]. The choice of antimicrobials is the same as for sporadic acute uncomplicated UTI (section 3.4.4.4).

3.5.4 Summary of evidence and recommendations for the diagnostic evaluation and treatment of rUTIs

Summary of evidence	LE
Extensive routine workup including cystoscopy, imaging, etc. has a low diagnostic yield for the diagnosis of rUTI.	3
Increased water intake is an effective antimicrobial-sparing strategy to prevent rUTI in premenopausal women at high risk for recurrence who drink low volumes (< 1.5 L) of fluid daily.	3
Vaginal oestrogen replacement has shown a trend towards preventing rUTI in post-menopausal women.	1b
Immunoactive prophylaxis has been shown to be more effective than placebo for in female patients with rUTIs in several randomised trials with a good safety profile.	1a
Probiotics containing L. rhamnosus GR-1, L. reuteri B-54 and RC-14, L. casei shirota, or L. crispatus CTV-05 are effective for vaginal flora restoration and have shown a trend towards prevention of rUTIs.	1b
Current scientific evidence regarding the efficacy of cranberry products in the prevention of UTIs is inconclusive.	1a
There is contradictory evidence on the efficacy of D-mannose to reduce the number of UTI episodes.	2
Based on limited evidence intravesical GAG therapy can reduce the number of UTIs per patient per year, and prolong the time interval between rUTI episodes.	2
A RCT demonstrated the non-inferiority of twice-daily methenamine hippurate to daily antibiotic prophylaxis.	1b
Both continuous low-dose antimicrobial prophylaxis and post-coital antimicrobial prophylaxis, have been shown to reduce the rate of rUTI.	1b
A prospective cohort study showed that intermittent self-start therapy is effective, safe and economical in women with rUTIs.	2b

Recommendations	Strength rating
Diagnose recurrent UTI by urine culture.	Strong
Do not perform an extensive routine workup (e.g., cystoscopy, full abdominal ultrasound) in women younger than 40 years of age with recurrent UTI and no risk factors.	Weak
Advise pre-menopausal women regarding increased fluid intake as it might reduce the risk of recurrent UTI.	Weak
Use vaginal oestrogen replacement in post-menopausal women to prevent recurrent UTI.	Strong
Use immunoactive prophylaxis to reduce recurrent UTI in all age groups.	Strong
Advise patients on the use of local or oral probiotic containing strains of proven efficacy for vaginal flora regeneration to prevent UTIs.	Weak
Advise patients on the use of cranberry products to reduce recurrent UTI episodes; however, patients should be informed that the quality of evidence underpinning this is low with contradictory findings.	Weak
Use D-mannose to reduce recurrent UTI episodes, but patients should be informed of the overall weak and contradictory evidence of its effectiveness.	Weak
Use methenamine hippurate to reduce recurrent UTI episodes in women without abnormalities of the urinary tract.	Strong
Use endovesical instillations of hyaluronic acid or a combination of hyaluronic acid and chondroitin sulphate to prevent recurrent UTIs in patients where less invasive preventive approaches have been unsuccessful. Patients should be informed that further studies are needed to confirm the results of initial trials.	Weak

Use continuous or post-coital antimicrobial prophylaxis to prevent recurrent UTI when non-antimicrobial interventions have failed. Counsel patients regarding possible side effects.	Strong
For patients with good compliance self-administered short-term antimicrobial therapy should be considered.	Strong

3.6 Uncomplicated pyelonephritis

Uncomplicated pyelonephritis is defined as pyelonephritis limited to non-pregnant, pre-menopausal women with no known relevant urological abnormalities or comorbidities.

*3.6.1 **Diagnostic evaluation***

3.6.1.1 Clinical diagnosis

Pyelonephritis is suggested by fever (> 38°C), chills, flank pain, nausea, vomiting, or costovertebral angle tenderness, with or without the typical symptoms of cystitis [207]. Pregnant women with acute pyelonephritis need special attention, as this kind of infection may not only have an adverse effect on the mother with anaemia, renal and respiratory insufficiency, but also on the unborn child with more frequent pre-term labour and birth [208].

3.6.1.2 Differential diagnosis

It is vital to differentiate as soon as possible between uncomplicated and complicated mostly obstructive pyelonephritis, as the latter can rapidly lead to urosepsis. This differential diagnosis should be made by the appropriate imaging technique (see section 3.6.1.4).

3.6.1.3 Laboratory diagnosis

Urinalysis including the assessment of white and red blood cells and nitrite, is recommended for routine diagnosis [209]. In addition, urine culture and antimicrobial susceptibility testing should be performed in all cases of pyelonephritis.

3.6.1.4 Imaging diagnosis

Evaluation of the upper urinary tract with ultrasound (US) should be performed to rule out urinary tract obstruction or renal stone disease in patients with a history of urolithiasis, renal function disturbances or a high urine pH [210]. Additional investigations, such as a contrast enhanced computed tomography (CT) scan, or excretory urography should be considered if the patient remains febrile after 72 hours of treatment, or immediately if there is deterioration in clinical status [210]. For diagnosis of complicating factors in pregnant women, US or magnetic resonance imaging (MRI) should be used preferentially to avoid radiation risk to the foetus [210].

*3.6.2 **Summary of evidence and recommendations for the diagnostic evaluation of uncomplicated pyelonephritis***

Summary of evidence	**LE**
Urine culture and antimicrobial susceptibility testing should be performed in all cases of pyelonephritis in addition to urinalysis.	4
A prospective observational cohort study found that radiologic imaging can selectively be applied in adults with febrile UTI without loss of clinically relevant information by using a simple clinical prediction rule.	2b
Additional imaging investigations, such as an unenhanced helical computed tomography should be done if the patient remains febrile after 72 hours of treatment or in patients with suspected complications e.g. sepsis.	4

Recommendations	**Strength rating**
Perform urinalysis (e.g. using the dipstick method), including the assessment of white and red blood cells and nitrite, for routine diagnosis.	Strong
Perform urine culture and antimicrobial susceptibility testing in patients with pyelonephritis.	Strong
Perform imaging of the urinary tract to exclude urgent urological disorders.	Strong

*3.6.3 **Disease management***

3.6.3.1 Outpatient treatment

Fluoroquinolones and cephalosporines are the only antimicrobial agents that can be recommended for oral empirical treatment of uncomplicated pyelonephritis [211]. However, oral cephalosporines achieve significantly lower blood and urinary concentrations than intravenous cephalosporines. Other agents such as nitrofurantoin, oral fosfomycin, and pivmecillinam should be avoided as there is insufficient data regarding their efficacy [212]. In the setting of fluoroquinolone hypersensitivity or known resistance, other acceptable choices include trimethoprim-sulfamethoxazole (160/800 mg) or an oral beta-lactam, if the uropathogen is known to be susceptible. If such agents are used in the absence of antimicrobial susceptibility results, an initial intravenous dose of a long-acting parenteral antimicrobial (e.g. ceftriaxone) should be administered. A short outpatient antibiotic course of treatment, for acute pyelonephritis, has been shown to be equivalent to longer durations of therapy in terms of clinical and microbiological success. However, this is associated with a higher recurrence rate of infection within four to six weeks and needs to be tailored to local policies and resistance patterns [213].

3.6.3.2 Inpatient treatment

Patients with uncomplicated pyelonephritis requiring hospitalisation should be treated initially with an intravenous antimicrobial regimen e.g. a fluoroquinolone, an aminoglycoside (with or without ampicillin), or an extended-spectrum cephalosporin or penicillin [214]. Ceftolozane/tazobactam achieved a clinical response rate of over 90% in patients with uncomplicated pyelonephritis [215, 216]. It also demonstrated significantly higher composite cure rates than levofloxacin among levofloxacin-resistant pathogens [217]. Ceftazidime-avibactam combination has been shown to be effective for treating ceftazidime-resistant *Enterobacterales* and *Pseudomonas aeruginosa* UTIs [218].

Novel antimicrobial agents include imipenem/cilastatin, cefiderocol, meropenem-vaborbactam and plazomicin. Imipenem/cilastatin has been investigated in a phase 2 randomised trial and showed good clinical response rates [219]. Cefatazidime-avibactam and doripenem showed similar efficacy against ceftazidime non-susceptible pathogens and may offer an alternative to carbapenems in this setting [220]. Meropenem-vaborbactam has been shown to be non-inferior to piperacillin-tazobactam in a phase 3 RCT [221]. It was also effective for treating carbapenem-resistant Enterobacterales with cure rates of 65% compared to best available treatment [222]. Once daily plazomicin was non-inferior to meropenem for the treatment of cUTIs and acute pyelonephritis caused by *Enterobacterales*, including multidrug-resistant strains [223]. Cefiderocol was non-inferior to imipenem/cilastatin for the treatment of complicated UTI in people with multidrug-resistant Gram-negative infections in a phase 2 RCT [224].

Carbapenems and novel broad spectrum antimicrobial agents should only be considered in patients with early culture results indicating the presence of multi-drug resistant organisms. The choice between these agents should be based on local resistance patterns and optimised on the basis of drug susceptibility results. In patients presenting with signs of urosepsis empiric antimicrobial coverage for ESBL-producing organisms is warranted [225]. Patients initially treated with parenteral therapy who improve clinically and can tolerate oral fluids may transition to oral antimicrobial therapy [226].

3.6.3.2.1 Summary of evidence and recommendations for the treatment of uncomplicated pyelonephritis

Summary of evidence	**LE**
Fluoroquinolones and cephalosporines are the only microbial agents that can be recommended for oral empirical treatment of uncomplicated pyelonephritis.	1b
Intravenous antimicrobial regimens for uncomplicated pyelonephritis may include a fluoroquinolone, an aminoglycoside (with or without ampicillin), or an extended-spectrum cephalosporin or penicillin.	1b
Carbapenems should only be considered in patients with early culture results indicating the presence of multi-drug resistant organisms.	4
The appropriate antimicrobial should be chosen based on local resistance patterns and optimised on the basis of drug susceptibility results.	3

Recommendations	**Strength rating**
Treat patients with uncomplicated pyelonephritis not requiring hospitalisation with short course fluoroquinolones as first-line treatment.	Strong
Treat patients with uncomplicated pyelonephritis requiring hospitalisation with an intravenous antimicrobial regimen initially.	Strong

Switch patients initially treated with parenteral therapy, who improve clinically and can tolerate oral fluids, to oral antimicrobial therapy.	Strong
Do not use nitrofurantoin, oral fosfomycin, and pivmecillinam to treat uncomplicated pyelonephritis.	Strong

Table 3: Suggested regimens for empirical oral antimicrobial therapy in uncomplicated pyelonephritis

Antimicrobial	Daily dose	Duration of therapy	Comments
Ciprofloxacin	500-750 mg b.i.d	7 days	Fluoroquinolone resistance should be less than 10%.
Levofloxacin	750 mg q.d	5 days	
Trimethoprim sulfamethoxazol	160/800 mg b.i.d	14 days	If such agents are used empirically, an initial intravenous dose of a long-acting parenteral antimicrobial (e.g. ceftriaxone) should be administered.
Cefpodoxime	200 mg b.i.d	10 days	
Ceftibuten	400 mg q.d	10 days	

b.i.d = twice daily; q.d = every day.

Table 4: Suggested regimens for empirical parenteral antimicrobial therapy in uncomplicated pyelonephritis

Antimicrobials	Daily dose	Comments
First-line treatment		
Ciprofloxacin	400 mg b.i.d	
Levofloxacin	750 mg q.d	
Cefotaxime	2 g t.i.d	Not studied as monotherapy in acute uncomplicated pyelonephritis.
Ceftriaxone	1-2 g q.d	Lower dose studied, but higher dose recommended.
Second-line treatment		
Cefepime	1-2 g b.i.d	Lower dose studied, but higher dose recommended.
Piperacillin/tazobactam	2.5-4.5 g t.i.d	
Gentamicin	5 mg/kg q.d	Not studied as monotherapy in acute uncomplicated pyelonephritis.
Amikacin	15 mg/kg q.d	
Last-line alternatives		
Imipenem/cilastatin	0.5 g t.i.d	Consider only in patients with early culture results indicating the presence of multi-drug resistant organisms.
Meropenem	1 g t.i.d	
Ceftolozane/tazobactam	1.5 g t.i.d	
Ceftazidime/avibactam	2.5 g t.i.d	
Cefiderocol	2g t.i.d	
Meropenem-vaborbactam	2g t.i.d	
Plazomicin	15mg/kg o.d	

b.i.d = twice daily; t.i.d = three times daily; q.d = every day; o.d = once daily.

In pregnant women with pyelonephritis, outpatient management with appropriate parenteral antimicrobials may also be considered, provided symptoms are mild and close follow-up is feasible [227, 228]. In more severe cases of pyelonephritis, hospitalisation and supportive care are usually required. After clinical improvement parenteral therapy can also be switched to oral therapy for a total treatment duration of seven to ten days. In men with febrile UTI, pyelonephritis, or recurrent infection, or whenever a complicating factor is suspected a minimum treatment duration of two weeks is recommended, preferably with a fluoroquinolone since prostatic involvement is frequent [229].

*3.6.4 **Follow-up***

Post-treatment urinalysis or urine cultures in asymptomatic patients post-therapy are not indicated.

3.7 Complicated UTIs

*3.7.1 **Introduction***

Complicated UTI (cUTI) occurs in an individual in whom factors related to the host (e.g. underlying diabetes or immunosuppression) or specific anatomical or functional abnormalities related to the urinary tract (e.g. obstruction, incomplete voiding due to detrusor muscle dysfunction) are believed to result in an infection that will be more difficult to eradicate than an uncomplicated infection [230-232]. New insights into the management of cUTIs also suggest to consider infections caused by multi-drug resistant uropathogens [233]. The underlying factors that are generally accepted to result in a cUTI are outlined in Table 5. The designation of cUTI encompasses a wide variety of underlying conditions that result in a remarkably heterogeneous patient population. Therefore, it is readily apparent that a universal approach to the evaluation and treatment of cUTIs is not sufficient, although there are general principles of management that can be applied to the majority of patients with cUTIs. The following recommendations are based on the Stichting Werkgroep Antibioticabeleid (SWAB) Guidelines from the Dutch Working Party on Antibiotic Policy [234].

Table 5: Common factors associated with complicated UTIs [233-236]

Obstruction at any site in the urinary tract	UTI in males
Foreign body	Pregnancy
Incomplete voiding	Diabetes mellitus
Vesicoureteral reflux	Immunosuppression
Recent history of instrumentation	Healthcare-associated infections
Isolated ESBL-producing organisms	Isolated multi-drug resistant organisms

*3.7.2 **Diagnostic evaluation***

3.7.2.1 Clinical presentation

A cUTI is associated with clinical symptoms (e.g. dysuria, urgency, frequency, flank pain, costovertebral angle tenderness, suprapubic pain and fever), although in some clinical situations the symptoms may be atypical for example, in NLUTD, CA-UTI or patients who have undergone radical cystectomy with urinary diversion. In addition, all patients with nephrostomy may have an atypical clinical presentation. Clinical presentation can vary from severe obstructive acute pyelonephritis with imminent urosepsis to a post-operative CA-UTI, which might disappear spontaneously as soon as the catheter is removed. Clinicians must also recognise that symptoms, especially lower urinary tract symptoms (LUTS), are not only caused by UTIs but also by other urological disorders, such as, for example, bladder outlet obstruction and autonomic dysfunction in patients with spinal lesions and NLUTD. Concomitant medical conditions, such as diabetes mellitus and renal failure, which can be related to urological abnormalities, are often also present in a cUTI.

3.7.2.2 Urine culture

Laboratory urine culture is the recommended method to determine the presence or absence of clinically significant bacteriuria in patients suspected of having a cUTI.

*3.7.3 **Microbiology (spectrum and antimicrobial resistance)***

A broad range of micro-organisms cause cUTIs. The spectrum is much larger than in uncomplicated UTIs and the bacteria are more likely to be resistant (especially in treatment-related cUTI) than those isolated in uncomplicated UTIs [235, 236]. *E. coli, Proteus spp., Klebsiella spp., Pseudomonas spp., Serratia spp.* and *Enterococcus spp.* are the most common species found in cultures. *Enterobacterales* predominate (60-75%), with *E. coli* as the most common pathogen; particularly if the UTI is a first infection. Otherwise, the bacterial spectrum may vary over time and from one hospital to another [237].

*3.7.4 **General principles of cUTI treatment***

Appropriate management of the urological abnormality or the underlying complicating factor is mandatory. Optimal antimicrobial therapy for cUTI depends on the severity of illness at presentation, as well as local resistance patterns and specific host factors (such as allergies). In addition, urine culture and susceptibility testing should be performed, and initial empirical therapy should be tailored and followed by (oral) administration of an appropriate antimicrobial agent on the basis of the isolated uropathogen.

3.7.4.1 Choice of antimicrobials

Considering the current resistance percentages of amoxicillin, co-amoxiclav, trimethoprim and trimethoprim-sulphamethoxazole, it can be concluded that these agents are not suitable for the empirical treatment of

pyelonephritis in a normal host and, therefore, also not for treatment of all cUTIs [238]. The same applies to ciprofloxacin and other fluoroquinolones in urological patients [238].

Patients with a UTI with systemic symptoms requiring hospitalisation should be initially treated with an intravenous antimicrobial regimen, such as an aminoglycoside with or without amoxicillin, or a second or third generation cephalosporin, or an extended-spectrum penicillin with or without an aminoglycoside [234]. The choice between these agents should be based on local resistance data, and the regimen should be tailored on the basis of susceptibility results [212]. These recommendations are not only suitable for pyelonephritis, but for all other cUTIs.

Alternative regimens for the treatment of cUTIs, particularly those caused by multidrug-resistant pathogens have been studied. Ceftolozane/tazobactam 1.5 g every eight hours demonstrated high clinical cure rates for cUTIs caused by ESBL-producing *Enterobacterales* in a pooled analysis of phase 3 clinical trials [239]. Cefiderocol (2 g) three times daily was non-inferior to imipenem-cilastatin (1 g) three times daily for the treatment of cUTI in patients with multidrug-resistant Gram-negative infections [224]. Imipenem/cilastatin plus relebactam (250 or 125 mg) was as effective as imipenem/cilastatin alone for treatment of cUTI in a phase 2 RCT [219]. Ceftazidime/avibactam has been shown to be as effective as carbapenems for the treatment of cUTI in a systematic review reporting a baseline of 25% for ESBL-producing *Enterobacterales*, but more severe adverse events were reported in the ceftazidime/avibactam group [240]. Once-daily plazomicin was shown to be non-inferior to meropenem for the treatment of cUTIs caused by *Enterobacterales,* including multidrug-resistant strains [223].

In view of the high degree of resistance, particularly among patients admitted to the department of urology, fluoroquinolones are not automatically suitable as empirical antimicrobial therapy, especially when the patient has used ciprofloxacin in the last six months [241]. Fluoroquinolones can only be recommended as empirical treatment when the patient is not seriously ill and it is considered safe to start initial oral treatment or if the patient has had an anaphylactic reaction to beta-lactam antimicrobials. Intravenous levofloxacin 750 mg once daily for five days has been shown to be non-inferior to a seven to fourteen days regimen of levofloxacin 500 mg once daily starting intravenously and switched to an oral regimen (based on mitigation of clinical symptoms) [242].

3.7.4.2 Duration of antimicrobial therapy

Treatment for seven [243] to fourteen days (for men fourteen days when prostatitis cannot be excluded) [244], is generally recommended, but the duration should be closely related to the treatment of the underlying abnormality. When the patient is hemodynamically stable and afebrile for at least 48 hours, a shorter treatment duration (e.g. seven days) may be considered in patients where a short-course treatment is desired due to relative-contraindications to the administered antibiotic [242].

*3.7.5 **Summary of evidence and recommendations for the treatment of complicated UTIs***

Summary of evidence	**LE**
Patients with a UTI with systemic symptoms requiring hospitalisation should be initially treated with an intravenous antimicrobial regimen chosen based on local resistance data and previous urine culture results from the patient, if available. The regimen should be tailored on the basis of susceptibility result.	1b
If the prevalence of fluoroquinolone resistance is thought to be < 10% and the patient has contraindications for third generation cephalosporins or an aminoglycoside, ciprofloxacin can be prescribed as an empirical treatment in women with complicated pyelonephritis.	2
In the event of hypersensitivity to penicillin a cephalosporins can still be prescribed, unless the patient has had systemic anaphylaxis in the past.	2
In patients with a cUTI with systemic symptoms, empirical treatment should cover ESBL if there is an increased likelihood of ESBL infection based on prevalence in the community, earlier collected cultures and prior antimicrobial exposure of the patient.	2
Intravenous levofloxacin 750 mg once daily for five days, is non-inferior to a seven to fourteen day regimen of levofloxacin 500 mg once daily starting intravenously and switched to an oral regimen (based on mitigation of clinical symptoms).	2

Recommendations	Strength rating
Use the combination of: • amoxicillin plus an aminoglycoside; • a second-generation cephalosporin plus an aminoglycoside; • a third-generation cephalosporin intravenously as empirical treatment of complicated UTI with systemic symptoms.	Strong
Only use ciprofloxacin provided that the local resistance percentages are < 10% when; • the entire treatment is given orally; • patients do not require hospitalisation; • patient has an anaphylaxis for beta-lactam antimicrobials.	Strong
Do not use ciprofloxacin and other fluoroquinolones for the empirical treatment of complicated UTI in patients from urology departments or when patients have used fluoroquinolones in the last six months.	Strong
Manage any urological abnormality and/or underlying complicating factors.	Strong

3.8 Catheter-associated UTIs

*3.8.1 **Introduction***

Catheter-associated UTI refers to UTIs occurring in a person whose urinary tract is currently catheterised or has been catheterised within the past 48 hours. The urinary catheter literature is problematic as many published studies use the term CA-bacteriuria without providing information on what proportion are CA-ABU and CA-UTI, and some studies use the term CA-UTI when referring to CA-ABU or CA-bacteriuria [235].

*3.8.2 **Epidemiology, aetiology and pathophysiology***

Catheter-associated UTIs are the leading cause of secondary healthcare-associated bacteraemia. Approximately 20% of hospital-acquired bacteraemias arise from the urinary tract, and the mortality associated with this condition is approximately 10% [245]. A multistate point-prevalence survey of 11,282 patients across 183 hospitals reported that UTI accounted for 12.9% of healthcare acquired infections [246]. The incidence of bacteriuria associated with indwelling catheterisation is 3-8% per day [247-251]. The duration of catheterisation is the most important risk factor for the development of a CA-UTI [252, 253]. A systematic review and meta-analysis reported an average CA-UTI incidence of 13.79/1000 hospitalised patients with a prevalence of 9.33% [254]. This study also demonstrated that patients at high risk for CA-UTI were female, had a prolonged duration of catheterisation, had diabetes and had longer hospital and intensive care unit (ICU) stays [254].

Urinary catheterisation perturbs host defence mechanisms and provides easier access of uropathogens to the bladder. Indwelling urinary catheters facilitate colonisation with uropathogens by providing a surface for the attachment of host cell binding receptors recognised by bacterial adhesins, thus enhancing microbial adhesion. In addition, the uroepithelial mucosa is damaged, exposing new binding sites for bacterial adhesins, and residual urine in the bladder is increased through pooling below the catheter bulb [255]. Catheter-associated UTIs are often polymicrobial and caused by multiple-drug resistant uropathogens.

*3.8.3 **Diagnostic evaluation***

3.8.3.1 Clinical diagnosis

Signs and systemic symptoms compatible with CA-UTI include new onset or worsening of fever, rigors, altered mental status, malaise, or lethargy with no other identified cause, flank pain, costovertebral angle tenderness, acute haematuria, pelvic discomfort and in those whose catheters have been removed dysuria, urgent or frequent urination and suprapubic pain or tenderness [234]. In the catheterised patient, the presence or absence of odorous or cloudy urine alone should not be used to differentiate CA-ABU from CA-UTI [234, 235].

3.8.3.2 Laboratory diagnosis

Microbiologically, CA-UTI is defined by microbial growth of ≥ 103 cfu/mL of one or more bacterial species in a single catheter urine specimen or in a mid-stream voided urine specimen from a patient whose urethral, suprapubic, or condom catheter has been removed within the previous 48 hours [235]. In catheterised patients, pyuria is not diagnostic for CA-UTI. The presence, absence, or degree of pyuria should not be used to differentiate CA-ABU from CA-UTI. Pyuria accompanying CA-ABU should not be interpreted as an indication for antimicrobial treatment. The absence of pyuria in a symptomatic patient suggests a diagnosis other than CA-UTI [235].

3.8.3.3 Summary of evidence table and recommendations for diagnostic evaluation of CA-UTI

Summary of evidence	LE
Patients with indwelling or suprapubic catheters become carriers of ABU, with antibiotic treatment showing no benefit.	1a
In the catheterised patient, the presence or absence of odorous or cloudy urine alone should not be used to differentiate CA-ABU from CA-UTI.	2
Microbiologically CA-UTI is defined by microbial growth of ≥ 10^3 cfu/mL of one or more bacterial species in a single catheter urine specimen or in a mid-stream voided urine specimen from a patient whose catheter has been removed within the previous 48 hours.	3

Recommendations	Strength rating
Do not carry out routine urine culture in asymptomatic catheterised patients.	Strong
Do not use pyuria as sole indicator for catheter-associated UTI.	Strong
Do not use the presence or absence of odorous or cloudy urine alone to differentiate catheter-associated asymptomatic bacteriuria from catheter-associated UTI.	Strong

3.8.4 ***Disease management***

3.8.4.1 Limiting catheterisation and appropriate catheter discontinuation

Indwelling catheters should be placed only when they are clinically indicated; for example, for management of urinary retention or where strict monitoring of fluid balance is required. Catheter restriction protocols are an important part of multi-modal interventions to reduce CA-UTI rates. Nurse-driven protocols in hospitals as well as community based multi-modal targeted infection programs have been proven to reduce CA-UTI rates [256, 257]. Adjunctive devices such as electronic reminder systems have also been shown to assist in prompt catheter removal in hospital settings (including non-ICU). A systematic review of nineteen different interventions to reduce UTI (including catheter discontinuation and limiting catheterisation), in nursing home patients reported successful CA-UTI reduction and reduced catheter usage [258]. Another report of over 2,800 patients on a surgical oncology unit found that increasing catheter bundle compliance resulted in a significant reduction in CA-UTI rates [259].

3.8.4.2 Urethral cleaning and chlorhexidine bathing

A network meta-analysis of 33 studies (6,490 patients) found no difference in the incidence of CA-UTI comparing the different urethral cleaning methods vs. disinfection [260]. The efficacy of chlorhexidine baths (either using 2% chlorhexidine-impregnated cloths or 4% chlorhexidine-based soap) in reducing CA-UTI is debatable. In a RCT of 10,783 ICU patients, no difference in CA-UTI rates were reported between chlorhexidine and control bathing groups [261]. However, a systematic review of fifteen studies involving only ICU patients reported that daily chlorhexidine bathing was associated with a significant reduction in CA-UTI (RR 0.68) [262].

3.8.4.3 Alternatives to indwelling urethral catheterisation

Alternatives include intermittent urethral catheterisation (IC) or suprapubic catheterisation. In a systematic review of patients undergoing gynaecological surgery, indwelling catheters were associated with higher rates of symptomatic UTIs compared to IC [263]. A further meta-analysis of post-partum women reported no difference in the incidence of UTI after labour between continuous catheterisation and IC [263]. A prospective cohort study of nursing home residents found that residents with a suprapubic catheter had fewer CA-UTIs and where hospitalised less, but were more likely to be colonised with multi drug resistant organisms [264].

A Cochrane Review found insufficient evidence to assess the value of different policies for replacing long-term urinary catheters on patient outcomes [98]. Another Cochrane review investigating the role of urethral (indwelling or intermittent) vs. suprapubic catheterisation in the short-term found inconclusive evidence of an effect on UTI rates [265]. For patients with NLUTD, a further systematic review found no randomised or quasi-randomised controlled trials and therefore no conclusions regarding the use of the different types of catheters could be made [266]. Therefore, based on the available literature, while there are some limited studies showing a benefit of IC or suprapubic catheterisation over urethral catheterisation for CA-UTI rates, there is insufficient evidence to recommend those approaches routinely [267].

3.8.4.4 Impregnated or coated catheters

Hydrophilic coated catheters have been found to be beneficial for reducing CA-UTI rates. A meta-analysis of seven studies investigating RCTs comparing hydrophilic coated to PVC (standard) catheters for IC found a statistically lower risk ratio (0.84) for the frequency of UTI in the hydrophilic catheter group [268]. A systematic review and practice policy statements on UTI prevention in patients with spina bifida recommended the use of single-use and hydrophilic catheters for IC [269].

Silver-alloy-impregnated catheters have not been associated with reduced CA-UTI rates. A small RCT of 54 ICU patients showed no significant difference in UTI rates between the silver-alloy impregnated group and the standard silicone foley catheter group [270]. In a cohort study of patients undergoing suprapubic catheter placement at the time of pelvic organ prolapsed surgery, a 5% difference in UTI rate at six weeks was noted, although this was not significant [271]. A systematic review of 26 trials (12,422 patients) reported that silver alloy-coated catheters were not associated with a statistically significant reduction in CA-UTI and were considerably more expensive [272]. However, the same study found that nitrofurazone-impregnated catheters reduce the risk of symptomatic CA-UTI; however, this was borderline significant (RR 0.84, 95% CI 0.71 to 0.99) [272]. A more recent RCT (214 patients) evaluating the use of nitrofurazone-infused catheters post-renal transplant found no benefit for their use [273]. Additionally, another RCT showed no benefit for the use of silver-alloy-coated indwelling catheters for reduction of UTI in 489 patients with spinal cord injury [274].

From a microbiological perspective, there may be a difference in organisms causing CA-UTI from urethral and suprapubic catheters and therefore urine culture results are important to guide therapy [267].

3.8.4.5 Antibiotic prophylaxis for catheter removal or insertion

The issue of whether antibiotic prophylaxis reduce the rate of symptomatic UTI in adults following indwelling bladder catheter removal has been the subject of multiple RCTs. A review and meta-analysis identified seven RCTs with 1,520 participants. Meta-analysis showed overall benefit for use of prophylaxis RR (95%CI) = 0.45 (0.28-0.72); ARR 5.8% (from 10.5% to 4.7%) with a number needed to treat (NNT) of 17 [214]. Results for individual trials were inconsistent with five trials including the possibility of no benefit [214]. In an affectional RCT with 172 participants undergoing laparoscopic radical prostatectomy randomised to seven days of ciprofloxacin (n=80) or no treatment (n=80) at the time of catheter removal, which occurred at a mean of nine days post-operatively, there was no difference in infective complications recorded at up to four weeks after catheter removal. More isolates obtained from the prophylaxis group (11) were resistant to ciprofloxacin compared to the no treatment group (3) [215]. With regards to catheter insertion, a systematic review and meta-analysis showed that prophylactic antibiotics reduced the rate of bacteriuria and other signs of infection, such as pyuria, fever and gram-negative isolates in patients' urine, in surgical patients who undergo bladder drainage for at least 24 hours post-operatively [275].

3.8.4.6 Antibiotic prophylaxis for intermittent self-catheterisation (ISC)

An RCT investigating the effect of antibiotic prophylaxis in patients performing ISC showed that the frequency of symptomatic antibiotic-treated UTI was reduced by 48% using prophylaxis in a cohort of 404 patients performing ISC [276]. However, resistance against the antibiotics used for UTI treatment was more frequent in urinary isolates from the prophylaxis group than in those from the control group at 9–12 months.

While the literature shows some benefit for reduction of CA-UTI by utilising antibiotics, the routine use of antibiotics for such a common procedure in the healthcare setting would result in an increased usage of antimicrobials. As highlighted in some of the RCTs this strategy is associated with increased antimicrobial resistance. Antibiotic use is the main driving force in the development of antimicrobial resistance. Current antimicrobial stewardship principles would not favour the routine use of antibiotic prophylaxis for either catheter changes or ISC even when UTIs could be prevented [267].

3.8.4.7 Antimicrobial treatment for suspected CA-UTI

A urine specimen for culture should be obtained prior to initiating antimicrobial therapy for presumed CA-UTI due to the wide spectrum of potential infecting organisms and the increased likelihood of antimicrobial resistance. The urine culture should be obtained from the freshly placed catheter prior to the initiation of antimicrobial therapy [235]. Based on the global prevalence on infections in urology (GPIU) study, the causative micro-organisms in CA-UTI are comparable with the causative micro-organisms in other cUTIs; therefore, symptomatic CA-UTIs should be treated according to the recommendations for cUTI (see section 3.7.5) [277].

Seven days is the recommended duration of antimicrobial treatment for patients with CA-UTI who have prompt resolution of symptoms, and fourteen days of treatment is recommended for those with a delayed response, regardless of whether the patient remains catheterised or not [235]. A five-day regimen of levofloxacin may be considered in patients with CA-UTI who are not severely ill. Data are insufficient to make such a recommendation about other fluoroquinolones. With the rise in fluoroquinolone resistance,

alternative antimicrobial agents should be selected where possible to start empirical therapy based on local microbiological information. A 5-day antibiotic regimen with catheter exchange has been shown in one study to be non-inferior to a 10-day regimen with catheter retention on the basis of clinical cure [278].

A three-day antimicrobial regimen may be considered for women aged ≤ 65 years who develop CA-UTI without upper urinary tract symptoms after an indwelling catheter has been removed. If an indwelling catheter has been in place for two weeks at the onset of CA-UTI and is still indicated, the catheter should be replaced to hasten resolution of symptoms and to reduce the risk of subsequent CA-bacteriuria and CA-UTI. If use of the catheter can be discontinued, a culture of a voided mid-stream urine specimen should be obtained prior to the initiation of antimicrobial therapy to help guide treatment [235]. Long-term indwelling catheters should not be changed routinely. Follow appropriate practices for catheter insertion and care [279].

3.8.4.8 Recommendations for disease management and prevention of CA-UTI

Summary of evidence	**LE**
A systematic review of nineteen different interventions to reduce UTI including catheter discontinuation and limiting catheterisation in nursing home patients reported successful CA-UTI reduction and reduced catheter usage.	1b
A meta-analysis of seven studies investigating RCTs comparing hydrophilic coated to PVC (standard) catheters for IC found a statistically lower risk ratio (0.84) for the frequency of UTI in the hydrophilic catheter group.	1a
A meta-analysis showed overall benefit for use of prophylaxis for reduction of infective complications after catheter removal; however, results from individual trials were inconsistent with five out of seven trials including the possibility of no benefit.	1a
A subsequent RCT found no benefit of antibiotic prophylaxis for reduction of infective complications at up to four weeks after catheter removal.	1b

Recommendations	**Strength rating**
Treat symptomatic catheter-associated-UTI according to the recommendations for complicated UTI (see section 3.7.5).	Strong
Take a urine culture prior to initiating antimicrobial therapy in catheterised patients in whom the catheter has been removed.	Strong
Do not treat catheter-associated asymptomatic bacteriuria in general.	Strong
Treat catheter-associated asymptomatic bacteriuria prior to traumatic urinary tract interventions (e.g. transurethral resection of the prostate).	Strong
Replace or remove the indwelling catheter before starting antimicrobial therapy.	Strong
Do not apply topical antiseptics or antimicrobials to the catheter, urethra or meatus.	Strong
Do not use prophylactic antimicrobials to prevent catheter-associated UTIs.	Strong
Do not routinely use antibiotic prophylaxis to prevent clinical UTI after urethral catheter removal.	Weak
The duration of catheterisation should be minimal.	Strong
Use hydrophilic coated catheters to reduce CA-UTI.	Strong
Do not routinely use antibiotic prophylaxis to prevent clinical UTI after urethral catheter removal or in patients performing intermittent self-catheterisation	Weak

3.9 Urosepsis

*3.9.1 **Introduction***

Patients with urosepsis should be diagnosed at an early stage, especially in the case of a cUTI. Systemic inflammatory response syndrome (SIRS), characterised by fever or hypothermia, leukocytosis or leukopenia, tachycardia and tachypnoea, has been recognised as a set of alerting symptoms [280, 281]; however, SIRS is no longer included in the recent terminology of sepsis (Table 6) [11]. Mortality is considerably increased the more severe the sepsis is.

The treatment of urosepsis involves adequate life-supporting care, appropriate and prompt antimicrobial therapy, adjunctive measures and the optimal management of urinary tract disorders [282]. Source control by decompression of any obstruction and drainage of larger abscesses in the urinary tract is essential [282]. Urologists are recommended to treat patients in collaboration with intensive care and infectious diseases specialists.

Urosepsis is seen in both community-acquired and healthcare associated infections. Nosocomial urosepsis may be reduced by measures used to prevent nosocomial infection, e.g. reduction of hospital stay, early removal of indwelling urinary catheters, avoidance of unnecessary urethral catheterisation, correct use of closed catheter systems, and attention to simple daily aseptic techniques to avoid cross-infection.

Sepsis is diagnosed when clinical evidence of infection is accompanied by signs of systemic inflammation, presence of symptoms of organ dysfunction and persistent hypotension associated with tissue anoxia (Table 6).

3.9.2 Epidemiology, aetiology and pathophysiology

Urinary tract infections can manifest from bacteriuria with limited clinical symptoms to sepsis or severe sepsis, depending on localised and potential systemic extension. It is important to note that a patient can move from an almost harmless state to severe sepsis in a very short time.

Mortality rates associated with sepsis vary depending on the organ source [283] with urinary tract sepsis generally having a lower mortality than that from other sources [284]. Sepsis is more common in men than in women [285]. In recent years, the overall incidence of sepsis arising from all sources has increased by 8.7% per year [283], but the associated mortality has decreased, which suggests improved management of patients (total in-hospital mortality rate fell from 27.8% to 17.9% from 1995 to 2000) [286]. Although the rate of sepsis due to Gram-positive and fungal organisms has increased, Gram-negative bacteria remain predominant in urosepsis [277, 287].

In urosepsis, as in other types of sepsis, the severity depends mostly upon the host response. Patients who are more likely to develop urosepsis include elderly patients, diabetics, immunosuppressed patients, such as transplant recipients and patients receiving cancer chemotherapy or corticosteroids. Urosepsis also depends on local factors, such as urinary tract calculi, obstruction at any level in the urinary tract, congenital uropathy, NLUTD, or endoscopic manoeuvres. However, all patients can be affected by bacterial species that are capable of inducing inflammation within the urinary tract.

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3.9.3 Diagnostic evaluation

For diagnosis of systemic symptoms in sepsis either the full Sequential [Sepsis-related] Organ Failure Assessment (SOFA) score, or the quickSOFA score should be applied (Table 6). Microbiology sampling should be applied to urine, two sets of blood cultures [288], and if appropriate drainage fluids. Imaging investigations, such as sonography and CT-scan should be performed early [289].

Table 6: Definition and criteria of sepsis and septic shock [11, 280, 281]

Disorder	Definition
Sepsis	Life-threatening organ dysfunction caused by a dysregulated host response to infection. For clinical application, organ dysfunction can be represented by an increase in the Sequential [Sepsis-related] Organ Failure Assessment (SOFA) score of 2 points or more. For rapid identification a quickSOFA (qSOFA) score was developed: respiratory rate of 22/min or greater, altered mentation, or systolic blood pressure of 100 mmHg or less.
Septic shock	Septic shock should be defined as a subset of sepsis in which particularly profound circulatory, cellular, and metabolic abnormalities are associated with a greater risk of mortality than with sepsis alone. Patients with septic shock can be clinically identified by a vasopressor requirement to maintain a mean arterial pressure of 65 mmHg or greater and serum lactate level greater than 2 mmol/L (>18 mg/dL) in the absence of hypovolemia.

*3.9.4 **Physiology and biochemical markers***

E. coli remains the most prevalent micro-organism. In several countries, bacterial strains can be resistant or multi-resistant and therefore difficult to treat [287]. Most commonly, the condition develops in compromised patients (e.g. those with diabetes or immunosuppression), with typical signs of generalised sepsis associated with local signs of infection.

3.9.4.1 Cytokines as markers of the septic response

Cytokines are involved in the pathogenesis of sepsis [284]. They are molecules that regulate the amplitude and duration of the host inflammatory response. They are released from various cells including monocytes, macrophages and endothelial cells, in response to various infectious stimuli. The complex balance between pro- and anti-inflammatory responses is modified in severe sepsis. An immunosuppressive phase follows the initial pro-inflammatory mechanism. Sepsis may indicate an immune system that is severely compromised and unable to eradicate pathogens or a non-regulated and excessive activation of inflammation, or both. Genetic predisposition is a probable explanation of sepsis in several patients. Mechanisms of organ failure and death in patients with sepsis remain only partially understood [284].

3.9.4.2 Biochemical markers

Procalcitonin is the inactive pro-peptide of calcitonin. Normally, levels are undetectable in healthy humans. During severe generalised infections (bacterial, parasitic and fungal) with systemic manifestations, procalcitonin levels rise [290]. In contrast, during severe viral infections or inflammatory reactions of non-infectious origin, procalcitonin levels show only a moderate or no increase. Mid-regional proadrenomedulline is another sepsis marker. Mid-regional proadrenomedullin has been shown to play a decisive role in the induction of hyperdynamic circulation during the early stages of sepsis and progression to septic shock [291]. Procalcitonin monitoring may be useful in patients likely to develop sepsis and to differentiate from a severe inflammatory status not due to bacterial infection [290, 292]. In addition, serum lactate is a marker of organ dysfunction and is associated with mortality in sepsis [293]. Serum lactate should therefore also be monitored in patients with severe infections.

*3.9.5 **Disease management***

3.9.5.1 Prevention

Septic shock is the most frequent cause of death for patients hospitalised for community-acquired and nosocomial infection (20-40%). Urosepsis treatment requires a combination of treatment including source control (obstruction of the urinary tract), adequate life-support care, and appropriate antimicrobial therapy [284, 289]. In such a situation, it is recommended that urologists collaborate with intensive care and infectious disease specialists for the best management of the patient.

3.9.5.1.1 Preventive measures of proven or probable efficacy

The most effective methods to prevent nosocomial urosepsis are the same as those used to prevent other nosocomial infections [294, 295] they include:

- Isolation of patients with multi-resistant organisms following local and national recommendations.
- Prudent use of antimicrobial agents for prophylaxis and treatment of established infections, to avoid selection of resistant strains. Antibiotic agents should be chosen according to the predominant pathogens at a given site of infection in the hospital environment.
- Reduction in hospital stay. Long inpatient periods before surgery lead to a greater incidence of nosocomial infections.
- Early removal of indwelling urethral catheters, as soon as allowed by the patient's condition. Nosocomial UTIs are promoted by bladder catheterisation as well as by ureteral stenting [296]. Antibiotic prophylaxis does not prevent stent colonisation, which appears in 100% of patients with a permanent ureteral stent and in 70% of those temporarily stented.
- Use of closed catheter drainage and minimisation of breaks in the integrity of the system, e.g. for urine sampling or bladder wash-out.
- Use of least-invasive methods to release urinary tract obstruction until the patient is stabilised.
- Attention to simple everyday techniques to assure asepsis, including the routine use of protective disposable gloves, frequent hand disinfection, and using infectious disease control measures to prevent cross-infections.

3.9.5.1.2 Appropriate peri-operative antimicrobial prophylaxis

For appropriate peri-operative antimicrobial prophylaxis see section 3.15. The potential side effects of antibiotics must be considered before their administration in a prophylactic regimen.

3.9.5.2 Treatment

Early goal-directed resuscitation was initially shown to improve survival for emergency department patients presenting with septic shock in a randomised, controlled, single-centre study [297]. However, follow-up studies in an improved emergency medicine background have not achieved positive effects with this strategy [298-300]. An individual patient data meta-analysis of the later three multicentre trials concluded that early goal-directed therapy did not result in better outcomes than usual care and was associated with higher hospitalisation costs [301].

3.9.5.2.1 Antimicrobial therapy

Initial empiric antimicrobial therapy should provide broad antimicrobial coverage against all likely causative pathogens and should be adapted on the basis of culture results, once available [282, 289]. The dosage of the antimicrobial substances is of paramount importance in patients with sepsis syndrome and should generally be high, with appropriate adjustment for renal function [282]. Antimicrobials must be administered no later than one hour after clinical assumption of sepsis [282].

3.9.5.2.2 Source control

Obstruction in the urinary tract is the most frequent urological source of urosepsis. Drainage of obstruction and abscesses, and removal of foreign bodies, such as urinary catheters or stones is therefore the most important source control strategy. These are key components of the strategy. This condition is an absolute emergency.

3.9.5.2.3 Adjunctive measures

The most important adjunctive measures in the management of sepsis are the following [282, 289]:

- fluid therapy with crystalloids, or albumin, if crystalloids are not adequately increasing blood pressure: passive leg raising-induced changes in cardiac output and in arterial pulse pressure are predictors of fluid responsiveness in adults [302];
- as vasopressors norepinephrine should be used primarily, dobutamine in myocardial dysfunction;
- hydrocortisone should be given only if fluid and vasopressors do not achieve a mean arterial pressure of ≥ 65 mmHg;
- blood products should be given to target a haemoglobin level of 7-9 g/dL;
- mechanical ventilation should be applied with a tidal volume 6 mL/kg and plateau pressure ≤ 30 cm H_2O and a high positive end-expiratory pressure;
- sedation should be given minimally, neuromuscular blocking agents should be avoided;
- glucose levels should be target at ≤ 180 mg/dL;
- deep vein thrombosis prevention should be given with low-molecular weight heparin subcutaneously;
- stress ulcer prophylaxis should be applied in patients at risk, using proton pump inhibitors;
- enteral nutrition should be started early (< 48 hours).

In conclusion, sepsis in urology remains a severe situation with a considerable mortality rate. A recent campaign, 'Surviving Sepsis Guidelines', aims to reduce mortality by 25% in the next years [282, 289, 303]. Early recognition of the symptoms may decrease the mortality by timely treatment of urinary tract disorders, e.g. obstruction, or urolithiasis. Adequate life-support measures and appropriate antimicrobial treatment provide the best conditions for improving patient survival. The prevention of sepsis is dependent on good practice to avoid nosocomial infections and using antimicrobial prophylaxis and therapy in a prudent and well-accepted manner.

3.9.5.3 Summary of evidence and recommendations for the diagnosis and treatment of urosepsis

Summary of evidence	**LE**
Initial high dose empiric antimicrobial therapy, administered within the first hour, should provide broad antimicrobial coverage against all likely causative pathogens and should be adapted on the basis of culture results, once available.	2b
Source control interventions should be implemented as soon as possible to control or eliminate diagnosed and/or suspected infectious foci.	3

Recommendations	**Strength rating**
Perform the quickSOFA score to identify patients with potential sepsis.	Strong
Take a urine culture and two sets of blood cultures before starting antimicrobial treatment.	Strong
Administer parenteral high dose broad spectrum antimicrobials within the first hour after clinical assumption of sepsis.	Strong

Adapt initial empiric antimicrobial therapy on the basis of culture results.	Strong
Initiate source control including removal of foreign bodies, decompression of obstruction and drainage of abscesses in the urinary tract.	Strong
Provide immediate adequate life-support measures.	Strong

Table 7: Suggested regimens for antimicrobial therapy for urosepsis.

Antimicrobials	Daily dose	Duration of therapy
Cefotaxime	2 g t.i.d	7-10 days Longer courses are appropriate in patients who have a slow clinical response
Ceftazidime	1-2 g t.i.d	
Ceftriaxone	1-2 g q.d	
Cefepime	2 g b.i.d	
Piperacillin/tazobactam	4.5 g t.i.d	
Ceftolozane/tazobactam	1.5 g t.i.d	
Ceftazidime/avibactam	2.5 g t.i.d	
Gentamicin*	5 mg/kg q.d	
Amikacin*	15 mg/kg q.d	
Ertapenem	1 g q.d	
Imipenem/cilastatin	0.5 g t.i.d	
Meropenem	1 g t.i.d	

** Not studied as monotherapy in urosepsis*
b.i.d = twice daily; t.i.d = three times daily; q.d = every day.

3.10 Urethritis

*3.10.1 **Introduction***

Urethritis can be of either infectious or non-infectious origin. Inflammation of the urethra presents usually with LUTS and must be distinguished from other infections of the lower urinary tract. Urethral infection is typically spread by sexual contact.

*3.10.2 **Epidemiology, aetiology and pathogenesis***

From a therapeutic and clinical point of view, gonorrhoeal urethritis (GU) caused by *Neisseria gonorrhoeae* must be differentiated from non-gonococcal urethritis (NGU). Non-gonococcal urethritis is a non-specific diagnosis that can have many infectious aetiologies. Causative pathogens include *Chlamydia trachomatis, Mycoplasma genitalium, Ureaplasma urealyticum* and *Trichomonas vaginalis.* The role of Ureaplasma spp. as urethritis causative pathogens is controversial. Recent data suggests that *U. urealyticum,* but not U. parvum is an aetiological agent in NGU [304]. The prevalence of isolated causative pathogens are: *C. trachomatis* 11-50%; *M. genitalium* 6-50%; *Ureaplasmas* 5-26%; *T. vaginalis* 1-20%; and adenoviruses 2-4% [305].

Causative agents either remain extracellularly on the epithelial layer or penetrate into the epithelium (*N. gonorrhoeae* and *C. trachomatis*) and cause pyogenic infection. Although arising from urethritis, chlamydiae and gonococci can spread further through the urogenital tract to cause epididymitis in men or cervicitis, endometritis and salpingitis in women [306].

Mucopurulent or purulent discharge, dysuria and urethral pruritus are symptoms of urethritis. However, many infections of the urethra are asymptomatic.

*3.10.3 **Evidence Summary***

A systematic search of the literature form January 2014 until February 2019 identified 488 titles of which 71 were selected for full text review. Thirteen systematic reviews or guidelines based on systematic literature searches [304-316], and seventeen original publications [317-333] were selected for further analysis. In addition, a further eleven relevant publications were identified from the references of the reviewed literature [334-344]. The evidence questions addressed were:

1. In patients with urethritis what is the best method of detecting the causative pathogen?
2. In patients with urethritis what are the best treatment strategies for clinical or microbiological cure?

3.10.4 ***Diagnostic evaluation***

In symptomatic patients the diagnosis of urethritis can be made based on the presence of any of the following criteria [305, 306]:

- Mucoid, mucopurulent, or purulent urethral discharge.
- Gram or methylene-blue stain of urethral secretions demonstrating inflammation. Five or more polymorphonuclear leucocytes (PMNL) per high power field (HPF) is the historical cut-off for the diagnosis of urethritis. A threshold of ≥ 2 PMNL/HPF was proposed recently based on better diagnostic accuracy [321, 334-336], but this was not supported by other studies [320]. Therefore, in line with the 2016 European Guideline on the management of NGU [305] the use of ≥ 5 PMNL/HPF cut-off level is recommended until the benefit of alternative cut-off levels is confirmed.
- The presence of ≥ 10 PMNL/HPF in the sediment from a spun first-void urine sample or a positive leukocyte esterase test in first-void urine.

Evidence of urethral inflammation in the Gram stain of urethral secretions with gonococci located intracellularly as Gram-negative diplococci indicates GU. Non-gonococcal urethritis is confirmed when staining of urethral secretions indicates inflammation in the absence of intracellular diplococci. Clinicians should always perform point-of-care diagnostics (e.g. Gram staining, first-void urine with microscopy, leukocyte esterase testing) if available to obtain objective evidence of urethral inflammation and to guide treatment [305, 306, 319]. Recent studies showed that processing time of point-of-care diagnostics is highly relevant in terms of patient compliance and real-life applicability [317, 318].

Men who meet the criteria for urethritis should be tested for *C. trachomatis, M. genitalium* and *N. gonorrhoea* with nucleic acid amplification tests (NAAT), even if point-of-care tests are negative for gonorrhoeae [305, 308]. The sensitivity and specificity of NAATs is better than that of any of the other tests available for the diagnosis of chlamydial and gonococcal infections [309, 337]. The performance of first-catch urine is non-inferior to urethral swabs [337]. In case of delayed treatment, if a NAAT is positive for gonorrhoea, a culture using urethral swabs should be performed before treatment to assess the antimicrobial resistance profile of the infective strain [306]. *N. gonorrhoeae* and *C. trachomatis* cultures are mainly used to evaluate treatment failures and monitor developing resistance to current treatment. Trichomonas spp. can usually be identified microscopically [306] or by NAATs [311].

Non-gonococcal urethritis is classified as persistent when symptoms do not resolve within three to four weeks following treatment. When this occurs NAATs should be performed for urethritis pathogens including *T. vaginalis* four weeks after completion of therapy [305, 322].

3.10.5 ***Disease management***

For severe urethritis empirical treatment should be started following diagnosis. If the patients symptoms are mild, delayed treatment guided by the results of NAATs is recommended. All sexual partners at risk should be assessed and treated whilst maintaining patient confidentiality [305, 325].

3.10.5.1 Gonococcal urethritis

For GU, a combination treatment using two antimicrobials with different mechanisms of action is recommended to improve treatment efficacy and to hinder increasing resistance to cephalosporins [306]. Ceftriaxone 1 g intramuscularly or intravenously with azithromycin 1 g single oral dose should be used as first-line treatment. Azithromycin is recommended because of its favourable susceptibility rates compared to other antimicrobials, good compliance with the single-dose regimen and the possibility of a C. trachomatis co-infection [306]. In case of azithromycin allergy, doxycycline can be used instead in combination with ceftriaxone or cefixime [306]. A 400 mg oral dose of cefixime is recommended as an alternative regimen to ceftriaxone; however, it has less favourable pharmacodynamics and may lead to the emergence of resistance [307, 343].

A number of alternative regimens for the treatment of GU have been studied. In a randomised, open label, non-comparative clinical study dual treatment with a combination of intramuscular gentamicin 240 mg plus oral azithromycin 2 g (n=202) single doses and a combination of oral gemifloxacin 320 mg plus oral azithromycin 2 g (n=199) single doses were associated with microbiological cure rates of 100% and 99.5%, respectively [339]. A 2014 systematic review focusing on the use of single-dose intramuscular gentamicin concluded that there is insufficient data to support or refute the efficacy and safety of this regimen in the treatment of uncomplicated gonorrhoea [313]. In three prospective single arm studies enrolling men with GU the use of extended-release azithromycin 2 g single oral dose resulted in microbiological cure rates of 83% (n=36), 93.8% (n=122) and 90.9% (n=33), respectively [329, 330, 332]. However, azithromycin monotherapy is generally not recommended because of its effect on increasing macrolide resistance rates [306]. Intramuscular spectinomycin 2 g single dose shows microbiological cure rates above 96% [340, 343] in urogenital gonorrhoeal infections; therefore, where available, it can be a valid treatment alternative. An open label, randomised trial compared oral fosfomycin trometamol 3 g

on days one, three and five (n=60) with intramuscular ceftriaxone 250 mg plus oral azithromycin 1 g single dose (n=61) in men with uncomplicated GU. In the per-protocol analysis clinical and microbiologic cure rates were 96.8% and 95.3% respectively [333].

The worldwide increase in gonorrhoeal antimicrobial resistance and the emergence of multidrug-resistant gonorrhoeal strains is a globally recognised healthcare crisis which emphasises the importance of guideline adherence [312, 324, 344].

3.10.5.2 Non-gonococcal urethritis

For NGU without an identified pathogen oral doxycycline 100 mg twice daily for seven days should be used as first-line treatment. Alternatively, single dose oral azithromycin 500 mg day one and 250 mg days two to four can be used. This regimen provides better efficacy compared to azithromycin 1 g single dose for *M. genitalium* infections, in which azithromycin 1 g single dose treatment is associated with the development of increasing macrolide resistance significantly decreasing the overall cure rate [305, 308, 314, 328]. However, a retrospective cohort study did not find significant difference between the extended and 1 g single dose azithromycin regimen regarding cure rates and the selection of macrolide resistance in *M. genitalium* urethritis [326]. If macrolide resistant *M. genitalium* is detected moxifloxacin 400 mg can be used for seven to fourteen days [305, 306, 315]. In case of failure after both azithromycin and moxifloxacin treatment, pristinamycin (registered in France) is the only antimicrobial agent with documented activity against *M. genitalium* [308, 327, 338]. Josamycin 500 mg three times a day for ten days is used in Russia, but will not eradicate macrolide-resistant strains [308].

For chlamydial urethritis azithromycin 1 g single dose and doxycycline 100 mg twice daily for seven days are both effective options [342]. A Cochrane Review found that in men with urogenital *C. trachomatis* infection regimens with azithromycin are probably less effective than doxycycline for microbiological failure, however, there might be little or no difference for clinical failure [316]. Fluoroquinolones, such as ofloxacin or levofloxacin, may be used as second-line treatment only in selected cases where the use of other agents is not possible [341].

For *U. urealyticum* infections the efficacy of doxycycline 100 mg twice daily for seven days is similar to azithromycin 1 g single dose treatment [305, 323]. For urethritis caused by *T. vaginalis* oral metronidazole or tinidazole 2 g single dose is recommended as first-line treatment. For treatment options for persistent or recurrent *T. vaginalis* infection refer to the review of Sena *et. al* [311].

In case of persistent NGU treatment should cover *M. genitalium* and *T. vaginalis* [305, 306].

*3.10.6 **Follow-up***

Patients should be followed up for control of pathogen eradication after completion of therapy only if therapeutic adherence is in question, symptoms persist or reoccurrence is suspected. Patients should be instructed to abstain from sexual intercourse for seven days after therapy is initiated, provided their symptoms have resolved and their sexual partners have been adequately treated. Reporting and source tracing should be done in accordance with national guidelines and in cooperation with specialists in venereology, whenever required. Persons who have been diagnosed with a new STD should receive testing for other STDs, including syphilis and HIV [310].

*3.10.7 **Summary of evidence and recommendations for the diagnostic evaluation and antimicrobial treatment of urethritis***

Summary of evidence	**LE**
A Gram stain of urethral discharge or a urethral smear that shows ≥ 5 leukocytes per high power field (× 1,000) and gonococci located intracellularly as Gram-negative diplococci, indicates gonococcal urethritis.	3b
Validated NAATs of first-void urine samples have better sensitivity and specificity than any of the other tests available for the diagnosis of chlamydial and gonococcal infections.	2a
For GU dual treatment with ceftriaxone and azithromycin is the most effective combination.	2a
In case of urogenital *C. trachomatis* infection in men azithromycin is probably less effective than doxycycline for microbiological failure, however, there might be little or no difference for clinical failure.	1a
In case of *U. urealyticum* infection the efficacy of doxycycline 100 mg twice for seven days is similar to azithromycin 1 g single dose treatment.	2a

Recommendations	Strength rating
Perform a Gram stain of urethral discharge or a urethral smear to preliminarily diagnose gonococcal urethritis.	Strong
Perform a validated nucleic acid amplification test (NAAT) on a first-void urine sample or urethral smear prior to empirical treatment to diagnose chlamydial and gonococcal infections.	Strong
Delay treatment until the results of the NAATs are available to guide treatment choice in patients with mild symptoms.	Strong
Perform a urethral swab culture, prior to initiation of treatment, in patients with a positive NAAT for gonorrhoea to assess the antimicrobial resistance profile of the infective strain.	Strong
Use a pathogen directed treatment based on local resistance data.	Strong
Sexual partners should be treated maintaining patient confidentiality.	Strong

Table 8: Suggested regimens for antimicrobial therapy for urethritis

Pathogen	Antimicrobial	Dosage & Duration of therapy	Alternative regimens
Gonococcal Infection	Ceftriaxone Azithromycin	1 g i.m. or i.v.*, SD 1 g p.o., SD	• Cefixime 400 mg p.o., SD plus Azithromycin 1 g p.o., SD In case of cephalosporin allergy: • Gentamicin 240 mg i.m SD plus Azithromycin 2 g p.o., SD • Gemifloxacin 320 mg p.o., SD plus Azithromycin 2 g p.o., SD • Spectinomycin 2 g i.m., SD • Fosfomycin trometamol 3 g p.o. on days 1, 3 and 5 In case of azithromycin allergy, in combination with ceftriaxone or cefixime: • Doxycycline 100 mg b.i.d, p.o., 7 days
Non-Gonococcal infection (non-identified pathogen)	Doxycycline	100 mg b.i.d, p.o., 7 days	Azithromycin 500 mg p.o., day 1, 250 mg p.o., 4 days
Chlamydia trachomatis	Azithromycin Or Doxycycline	1.0-1.5 g p.o., SD 100 mg b.i.d, p.o., for 7 days	• Levofloxacin 500 mg p.o., q.d., 7 days • Ofloxacin 200 mg p.o., b.i.d., 7 days
Mycoplasma genitalium	Azithromycin	500 mg p.o., day 1, 250 mg p.o., 4 days	In case of macrolide resistance: • Moxifloxacin 400 mg q.d., 7-14 days
Ureaplasma urealyticum	Doxycycline	100 mg b.i.d, p.o., 7 days	Azithromycin 1.0-1.5 g p.o., SD
Trichomonas vaginalis	Metronidazole Tinidazole	2 g p.o., SD 2 g p.o., SD	Metronidazole 500 mg p.o., b.i.d., 7 days
Persistent non-gonococcal urethritis			
After first-line doxycycline	Azithromycin plus Metronidazole	500 mg p.o., day 1, 250 mg p.o., 4 days 400 mg b.i.d. p.o., 5 days	If macrolide resistant *M. genitalium* is detected moxifloxacin should be substituted for azithromycin

After first-line azithromycin	Moxifloxacin plus Metronidazole	400 mg p.o. q.d., 7-14 days 400 mg b.i.d. p.o., 5 days	

SD = single dose; b.i.d = twice daily; q.d = everyday; p.o. = orally; i.m. = intramuscular; i.v. = intravenous.
** Despite the lack of RCTs there is increasing evidence that intravenous treatment with ceftriaxone is safe and effective for the treatment of gonorrhoeal infections and avoids the discomfort of an intramuscular injection for patients [345].*

3.11 Bacterial Prostatitis

*3.11.1 **Introduction***

Bacterial prostatitis is a clinical condition caused by bacterial pathogens. It is recommended that urologists use the classification suggested by the National Institute of Diabetes, Digestive and Kidney Diseases (NIDDK) of the National Institutes of Health (NIH), in which bacterial prostatitis, with confirmed or suspected infection, is distinguished from chronic pelvic pain syndrome (CPPS) (Table 9) [346-348].

Table 9: Classification of prostatitis and CPPS according to NIDDK/NIH [346-348]

Type	Name and description
I	Acute bacterial prostatitis (ABP)
II	Chronic bacterial prostatitis (CBP)
III	Chronic non-bacterial prostatitis – CPPS
IIIA	Inflammatory CPPS (white cells in semen/EPS/VB3)
IIIB	Non-inflammatory CPPS (no white cells in semen/EPS/VB3)
IV	Asymptomatic inflammatory prostatitis (histological prostatitis)

CPPS = chronic pelvic pain syndrome; EPS = expressed prostatic secretion; VB3 = voided bladder urine specimen 3 (urine following prostatic massage).

*3.11.2 **Evidence Summary***

A systematic literature search from 1980 until June 2017 was performed. One systematic review [349], six RCTs [350-355], two narrative reviews [356, 357], one prospective cohort study [358], two prospective cross-sectional studies [359, 360], and one retrospective cohort study [352], were selected from 856 references.

A retrospective study [361], investigated the potential role of unusual pathogens in prostatitis syndrome in 1,442 patients over a four-year period. An infectious aetiology was determined in 74.2% of patients; *C. trachomatis*, *T. vaginalis* and *U. urealyticum* infections were found in 37.2%, 10.5% and 5% of patients, respectively whilst *E. coli* infection was found in only 6.6% of cases. Cross sectional studies confirmed the validity of the Meares and Stamey test to determine the bacterial strain and targeted antibiotic therapies [359, 360]. The evidence levels were good, in particular those regarding information on atypical strains, epidemiology and antibiotic treatments.

A systematic review on antimicrobial therapy for CBP [349] compared multiple antibiotic regimens from eighteen selected studies enrolling a total of 2,196 patients. The role of fluoroquinolones as first line agents was confirmed with no significant differences between levofloxacin, ciprofloxacin and prulifloxacin in terms of microbiological eradication, clinical efficacy and adverse events. The efficacy of macrolides and tetracyclines on atypical pathogens was confirmed.

Randomised controlled trials on combined treatments [354, 355] indicated that the combination of plants/herbal extracts or PDE5Is with antibiotics may improve quality of life and symptoms in patients with CBP; however, the number of enrolled patients was inadequate to obtain definitive conclusions.

A review of treatment of bacterial prostatitis [356] indicated that the treatment of CBP is hampered by the lack of an active antibiotic transport mechanism into infected prostate tissue and fluids. The review underlined the potential effect of different compounds in the treatment of ABP and CBP on the basis of over 40 studies on the topic.

One RCT compared the effects of two different metronidazole regimens for the treatment of CBP caused by *T. vaginalis* [353]. Metronidazole 500 mg three times daily for fourteen days was found to be efficient for micro-organism eradication in 93.3% of patients with clinical failure in 3.33% of cases. The evidence question addressed was: In men with NIDDK/NIH Category I or II prostatitis what is the best antimicrobial treatment strategy for clinical resolution and eradication of the causative pathogen?

*3.11.3 **Epidemiology, aetiology and pathogenesis***

Prostatitis is a common diagnosis, but less than 10% of cases have proven bacterial infection [228]. *Enterobacterales*, especially *E. coli*, are the predominant pathogens in ABP [362]. In CBP, the spectrum of species is wider and may include atypical micro-organisms [356]. In patients with immune deficiency or HIV infection, prostatitis may be caused by fastidious pathogens, such as *M. tuberculosis*, *Candida spp.* and other rare pathogens, such as *Coccidioides immitis*, *Blastomyces dermatitidis,* and *Histoplasma capsulatum* [363]. The significance of identified intracellular bacteria, such as *C. trachomatis,* is uncertain [364]; however, two studies have highlighted its possible role as a causative pathogen in CBP [365, 366].

*3.11.4 **Diagnostic evaluation***

3.11.4.1 History and symptoms

Acute bacterial prostatitis usually presents abruptly with voiding symptoms and distressing but poorly localised pain. It is often associated with malaise and fever. Transrectal prostate biopsy increases the risk of ABP despite antibiotic prophylaxis and antiseptic prevention procedures [350]. Chronic bacterial prostatitis is defined by symptoms that persist for at least three months [367-369]. The predominant symptoms are pain at various locations including the perineum, scrotum, penis and inner part of the leg as well as LUTS [346-348].

3.11.4.2 Symptom questionnaires

In CBP symptoms appear to have a strong basis for use as a classification parameter [370]. Prostatitis symptom questionnaires have therefore been developed to assess severity and response to therapy [370, 371]. They include the validated Chronic Prostatitis Symptom Index (CPSI); however, its usefulness in clinical practice is uncertain [358].

3.11.4.3 Clinical findings

In ABP, the prostate may be swollen and tender on DRE. Prostatic massage should be avoided as it can induce bacteraemia and sepsis. Urine dipstick testing for nitrite and leukocytes has a positive predictive value of 95% and a negative predictive value of 70% [372]. Blood culture and complete blood count are useful in ABP. Imaging studies can detect a suspected prostatic abscess [356].

In case of longer lasting symptoms CPPS as well as other urogenital and anorectal disorders must be taken into consideration. Symptoms of CBP or CPPS can mask prostate tuberculosis. Pyospermia and hematospermia in men in endemic regions or with a history of tuberculosis should trigger investigation for urogenital tuberculosis.

3.11.4.4 Urine cultures and expressed prostatic secretion

The most important investigation in the evaluation of a patient with ABP is mid-stream urine culture [356]. In CBP, quantitative bacteriological localisation cultures and microscopy of the segmented urine and expressed prostatic secretion (EPS), as described by Meares and Stamey [373], are still important investigations to categorise clinical prostatitis [359, 360]. Accurate microbiological analysis of samples from the Meares and Stamey test may also provide useful information on the presence of atypical pathogens such as *C. trachomatis, T. vaginalis* and *U. urealiticum* [361]. The two-glass test has been shown to offer similar diagnostic sensitivity to the four-glass test [374].

3.11.4.5 Prostate biopsy

Prostate biopsies cannot be recommended as routine work-up and are not advisable in patients with untreated bacterial prostatitis due to the increased risk of sepsis.

3.11.4.6 Other tests

Transrectal US may reveal endoprostatic abscesses, calcification in the prostate, and dilatation of the seminal vesicles; however, it is unreliable as a diagnostic tool for prostatitis [375].

3.11.4.7 Additional investigations

3.11.4.7.1 Ejaculate analysis

Performing an ejaculated semen culture improves the diagnostic utility of the four-glass test [359]; however, semen cultures are more often positive than EPS cultures in men with non-bacterial prostatitis [360]. Bladder outflow and urethral obstruction should always be considered and ruled out by uroflowmetry, retrograde urethrography, or endoscopy.

3.11.4.7.2 First-void urine sample

First-void urine is the preferred specimen for the diagnosis of urogenital C. trachomatis infection in men by NAATs, since it is non-invasive and yet allows the detection of infected epithelial cells and associated *C. trachomatis* particles [376].

3.11.4.7.3 Prostate specific antigen (PSA)

Prostate specific antigen is increased in about 60% and 20% of men with ABP and CBP, respectively [357]. The PSA level decreases after antibiotic therapy (which occurs in approximately 40% of patients) and correlates with clinical and microbiological improvement [351]. Measurement of free and total PSA adds no practical diagnostic information in prostatitis [377].

3.11.4.8 Summary of evidence and recommendations for the diagnosis of bacterial prostatitis

Summary of evidence	**LE**
Urine dipstick testing for nitrite and leukocytes has a positive predictive value of 95% and a negative predictive value of 70% in patients with ABP.	3
The four-glass Meares and Stamey test is the optimum test for diagnosis of CBP. The two-glass test has been shown to offer similar diagnostic sensitivity in a comparison study.	2b
First-void urine is the preferred specimen for the diagnosis of urogenital C. trachomatis infection in men by NAATs.	2b
Transrectal ultrasound is unreliable and cannot be used as a diagnostic tool in prostatitis.	3
Semen culture sensitivity is reported to be approximately 50%; therefore, it is not routinely part of the diagnostic assessment of CBP.	3
Prostate specific antigen levels may be elevated during active prostatitis; therefore, PSA testing should be avoided as it offers no practical diagnostic information for prostatitis.	3

Recommendations	**Strength rating**
Do not perform prostatic massage in acute bacterial prostatitis (ABP).	Strong
Take a mid-stream urine dipstick to check nitrite and leukocytes in patients with clinical suspicion of ABP.	Weak
Take a mid-stream urine culture in patients with ABP symptoms to guide diagnosis and tailor antibiotic treatment.	Weak
Take a blood culture and a total blood count in patients presenting with ABP.	Weak
Perform accurate microbiological evaluation for atypical pathogens such as Chlamydia *trachomatis* or Mycoplasmata in patients with chronic bacterial prostatitis (CBP).	Weak
Perform the Meares and Stamey 2- or 4-glass test in patients with CBP.	Strong
Perform transrectal ultrasound in selected cases to rule out the presence of prostatic abscess.	Weak
Do not routinely perform microbiological analysis of the ejaculate alone to diagnose CBP.	Weak

3.11.5 ***Disease management***

3.11.5.1 Antimicrobials

Antimicrobials are life-saving in ABP and recommended in CBP. Culture-guided antibiotic treatments are the optimum standard; however, empirical therapies should be considered in all patients with ABP.

In ABP parenteral administration of high doses of bactericidal antimicrobials, such as broad-spectrum penicillins, a third-generation cephalosporin or fluoroquinolones, is recommended [378]. For initial therapy, any of these antimicrobials may be combined with an aminoglycoside [362-371, 378-382]. Ancillary measures include adequate fluid intake and urine drainage [228]. After normalisation of infection parameters, oral therapy can be substituted and continued for a total of two to four weeks [383].

Fluoroquinolones, despite the high resistance rates of uropathogens, are recommended as first-line agents in the empirical treatment of CBP because of their favourable pharmacokinetic properties [384], their generally good safety profile and antibacterial activity against Gram-negative pathogens including *P. aeruginosa* and *C. trachomatis* [349, 385]. However, increasing bacterial resistance is a concern. Azithromycin and doxycycline are active against atypical pathogens such as *C. trachomatis* and genital mycoplasmata [352, 361]. Levofloxacin did not demonstrate significant clearance of *C. trachomatis* in patients with CBP [386]. Metronidazole treatment is indicated in patients with *T. vaginalis* infections [353].

Duration of fluoroquinolone treatment must be at least fourteen days while azithromycin and doxycycline treatments should be extended to at least three to four weeks [352, 361]. In CBP antimicrobials should be given for four to six weeks after initial diagnosis [356]. If intracellular bacteria have been detected macrolides or tetracyclines should be given [349, 384, 387].

3.11.5.2 Intraprostatic injection of antimicrobials

This treatment has not been evaluated in controlled trials and should not be considered [388, 389].

3.11.5.3 Combined treatments

A combination of fluoroquinolones with various herbal extracts may attenuate clinical symptoms without increasing the rate of adverse events [354]. However, a combination of fluoroquinolones with vardenafil did not improve microbiological eradication rates or attenuated pain or voiding symptoms in comparison with fluoroquinolone treatment alone [355].

3.11.5.4 Drainage and surgery

Approximately 10% of men with ABP will experience urinary retention [390] which can be managed by urethral or suprapubic catheterisation. However, recent evidence suggests that suprapubic catheterisation can reduce the risk of development of CBP [391].

In case of prostatic abscess, both drainage and conservative treatment strategies appear feasible [392]; however, the abscess size may matter. In one study, conservative treatment was successful if the abscess cavities were < 1 cm in diameter, while larger abscesses were better treated by single aspiration or continuous drainage [393].

3.11.5.5 Summary of evidence and recommendations for the disease management of bacterial prostatitis

Summary of evidence	**LE**
The treatment regimen for ABP is based on clinical experience and a number of uncontrolled clinical studies. For systemically ill patients with ABP, parenteral antibiotic therapy is preferable. After normalisation of infection parameters, oral therapy can be substituted and continued for a total of two to four weeks.	3
The role of fluoroquinolones as first-line agents for antimicrobial therapy for CBP was confirmed in a systematic review, with no significant differences between levofloxacin, ciprofloxacin and prulifloxacin in terms of microbiological eradication, clinical efficacy and adverse events.	1a
Metronidazole 500 mg three times daily for fourteen days was found to be efficient for eradication in 93.3% of patients with T. vaginalis CBP.	1b
In patients with CBP caused by obligate intracellular pathogens, macrolides showed higher microbiological and clinical cure rates compared to fluoroquinolones.	1a
Clinicians should consider local drug-resistance patterns when choosing antibiotics.	3

Recommendations	Strength rating
Acute bacterial prostatitis	
Treat acute bacterial prostatitis according to the recommendations for complicated UTIs (see section 3.7.5).	Strong
Chronic bacterial prostatitis (CBP)	
Prescribe a fluoroquinolone (e.g. ciprofloxacin, levofloxacin) as first-line treatment for CBP.	Strong
Prescribe a macrolide (e.g. azithromycin) or a tetracycline (e.g. doxycycline) if intracellular bacteria have been identified as the causative agent of CBP.	Strong
Prescribe metronidazole in patients with T. vaginalis CBP.	Strong

Table 10: Suggested regimens for antimicrobial therapy for chronic bacterial prostatitis

Antimicrobial	Daily dose	Duration of therapy	Comments
Fluoroquinolone	Optimal oral daily dose	4-6 weeks	
Doxycycline	100 mg b.i.d	10 days	Only for *C. trachomatis* or mycoplasma infections
Azithromycin	500 mg once daily	3 weeks	Only for *C. trachomatis* infections
Metronidazole	500 mg t.i.d.	14 days	Only for *T. vaginalis* infections

b.i.d = twice daily; t.i.d = three times daily.

*3.11.6 **Follow-up***

In asymptomatic post-treatment patients routine urinalysis and/or urine culture is not mandatory as there are no validated tests of cure for bacterial prostatitis except for cessation of symptoms [356]. In patients with persistent symptoms and repeated positive microbiological results for sexually transmitted infectious pathogens, microbiological screening of the patient's partner/s is recommended. Antibiotic treatments may be repeated with a more prolonged course, higher dosage and/or different compounds [356].

3.12 Acute Infective Epididymitis

*3.12.1 **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 [394]. 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 that can be identified by appropriate diagnostics in up to 90% of patients [395]. Torsion of the spermatic cord (testicular torsion) is the most important differential diagnosis in boys and young men.

The predominant pathogens isolated are *Enterobacterales* (typically *E. coli*), *C. trachomatis* and *N. gonorrhoeae* [396]. Men who have anal intercourse and those with abnormalities of the urinary tract resulting in bacteriuria are at higher risk of epididymitis caused by *Enterobacterales* [397]. The mumps virus should be considered if there are viral prodromal symptoms and salivary gland enlargement. Tuberculous epididymitis may occur, typically as chronic epididymitis, 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 spp.* are rare possible pathogens.

*3.12.2 **Diagnostic Evaluation***

Culture of a mid-stream specimen of urine should be performed and any previous urine culture results should be checked. Sexually transmitted infections including *C. trachomatis* or *N. gonorrhoeae* should be detected by NAAT on first voided urine or urethral swab. A urethral swab or smear should be performed for Gram staining and culture of *N. gonorrhoeae,* when available [394, 398, 399]. Detection of these pathogens should be reported according to local procedures. All patients with probable sexually transmitted infections (STIs) should be advised to attend an appropriate clinic to be screened for other STIs. Men with *Enterobacterales* may require investigation for lower urinary tract abnormalities. If tuberculous epididymitis is suspected, three sequential early morning urine samples should be cultured for acid-fast bacilli (AFB) and sent for screening by NAAT for *M. tuberculosis* DNA [400]. If appropriate 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. Scrotal ultrasound is more accurate for the diagnose of acute epididymitis than urinalysis alone [401] and may also be beneficial for the exclusion of other pathologies [402].

3.12.3 ***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 with consideration of the most probable pathogen and degree of penetration into the inflamed epididymis and may need to be varied according to local pathogen sensitivities and guidance. Generally, both *C. trachomatis* and *Enterobacterales* should be covered initially and the regimen modified according to pathogen identification. Doxycycline and some specific fluoroquinolones have good clinical and microbiological cure rates in patients with suspected *C. trachomatis* or *M. genitalium* and both achieve adequate levels in inflamed male genital tissues with oral dosing. Macrolide antibiotics such as azithromycin are effective against *C. trachomatis* but have not been tested in epididymitis; however, initial pharmacokinetic studies suggest that azithromycin may effectively penetrate epididymal tissue when given in multiple doses [403]. Fluoroquinolones remain effective for oral treatment of *Enterobacterales* although resistance is increasing and local advice should be sought. Fluoroquinolones should not be considered for gonorrhoea. Single high parenteral dose of a third-generation cephalosporin is effective against *N. gonorrhoeae;* current resistance patterns and local public health recommendations should guide choice of agent.

Clinical response to antibiotics in men with severe epididymitis should be assessed after approximately three days. Men with likely or proven STI should be assessed at fourteen days to check cure and ensure tracing and treatment of contacts according to local public health recommendations.

3.12.4 ***Evidence Summary***

Relating to this chapter, four guidelines based on systematic reviews were identified [306, 398, 404, 405]. No evidence quality assessments were detailed. A high quality RCT demonstrated that a ten-day course of ciprofloxacin was superior to pivampicillin for clinical cure (80% vs. 60%) in men aged > 40 years [406]. Data from a large comparative case series suggested that young age and history of sexual activity are not sufficiently predictive of a sexually transmitted pathogen to guide antibiotic treatment in acute epididymitis [395].

Empiric antibiotic regimens from existing guidelines [306, 398, 404, 405] and panel consensus:

1. For men with acute epididymitis at low risk of gonorrhoea (e.g. no discharge) a single agent or combination of two agents of sufficient dose and duration to eradicate *C. trachomatis* and *Enterobacterales* should be used. Appropriate options are:

    A. A fluoroquinolone active against *C. trachomatis* orally once daily for ten to fourteen days*

    OR

    B. Doxycycline 200 mg initial dose by mouth and then 100 mg twice daily for ten to fourteen days* **plus** an antibiotic active against *Enterobacterales*** for ten to fourteen days*

2. For men with likely gonorrhoeal acute epididymitis a combination regimen active against Gonococcus and *C. trachomatis* must be used such as:

    A. Ceftriaxone 1000 mg intramuscularly single dose **plus** doxycycline 200 mg initial dose by mouth and then 100 mg twice daily for ten to fourteen days*

3. For non-sexually active men with acute epididymitis a single agent of sufficient dose and duration to eradicate *Enterobacterales* should be used. Appropriate option is a fluoroquinolone by mouth once daily for ten to fourteen days*

**Depending upon pathogen identification and clinical response.*
*** A parenteral option will be required for men with severe infection requiring hospitalisation.*

Surgical exploration may be required to drain abscesses or debride tissue. A comparative cohort study found that lack of separation of epididymis and testis on palpation and the presence of abscess on US may predict requirement for surgery following initial antibiotic treatment [407].

A cohort study found semen parameters may be impaired during epididymitis but recovered following successful treatment [408]. Comparative clinician cohort studies suggest adherence to guidelines for assessment and treatment of epididymitis is low, particularly by urologists compared to sexual health specialists [409] and by primary care physicians [410].

3.12.5 ***Screening***

A large cohort screening study for carriage of C. trachomatis including a randomly selected group of 5,000 men of whom 1,033 were tested showed no benefit in terms of reduction in risk of epididymitis over nine years of observation [411].

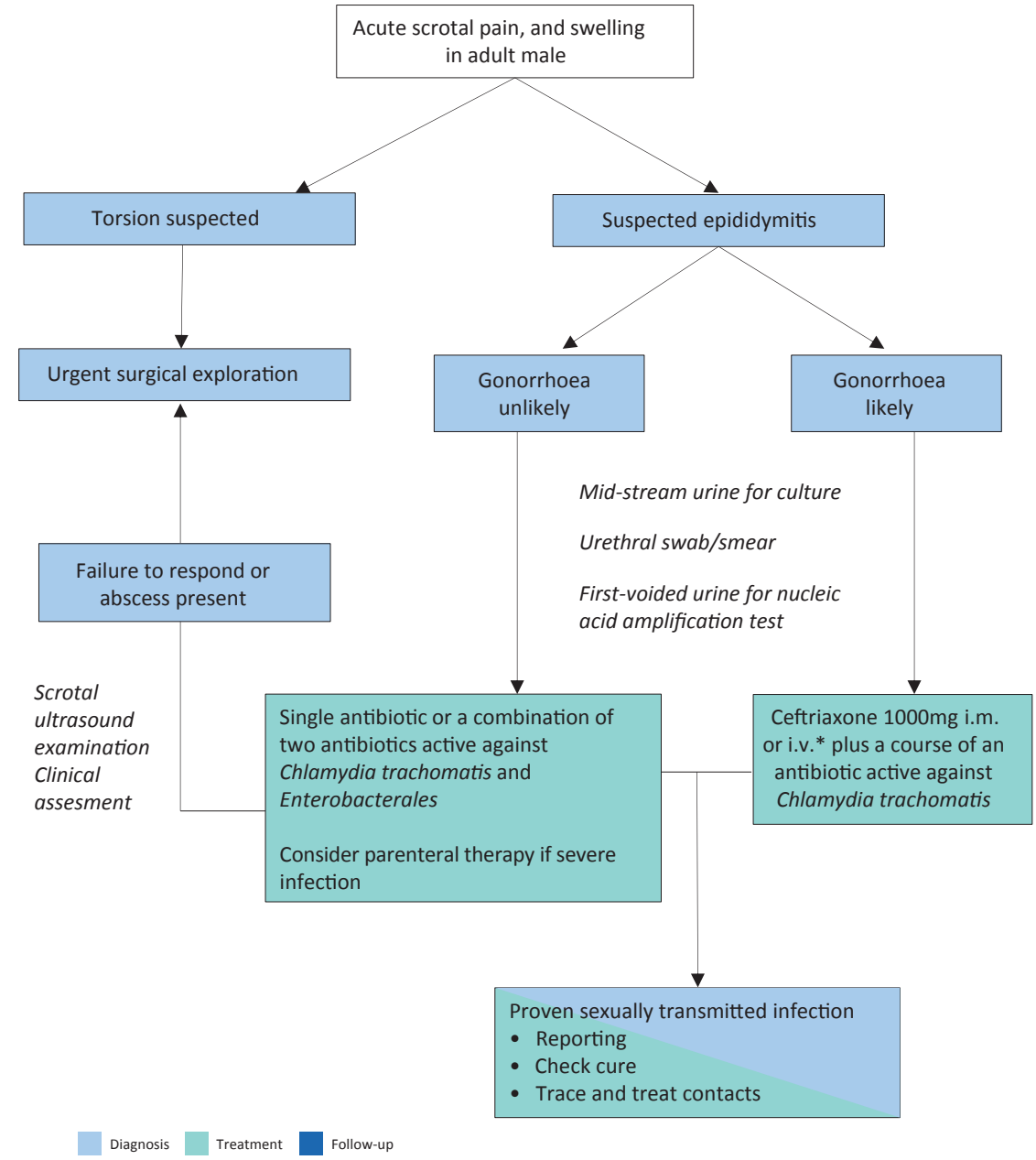
3.12.6 *Summary of evidence and recommendations for the diagnosis and treatment of acute infective epididymitis*

Summary of evidence	LE
In young sexually active patients both STIs and Enterobacterales have to be considered as aetiological agents.	3
In patients > 40 years antibiotic therapy with ciprofloxacin is superior to pivmecillinam.	1b
A negative sexual risk history does not exclude STIs in sexually active men.	3

Recommendations	Strength rating
Obtain a mid-stream urine and a first voided urine for pathogen identification by culture and nucleic acid amplification test.	Strong
Initially prescribe a single antibiotic or a combination of two antibiotics active against Chlamydia trachomatis and Enterobacterales in young sexually active men; in older men without sexual risk factors only Enterobacterales have to be considered.	Strong
If gonorrhoeal infection is likely give single dose ceftriaxone 1000 mg intramuscularly or intravenously* in addition to a course of an antibiotic active against Chlamydia trachomatis.	Strong
Adjust antibiotic agent when pathogen has been identified and adjust duration according to clinical response.	Weak
Follow national policies on reporting and tracing/treatment of contacts for sexually transmitted infections.	Strong

**Despite the lack of RCTs there is increasing evidence that intravenous treatment with ceftriaxone is safe and effective for the treatment of gonorrhoeal infections and avoids the discomfort of an intramuscular injection for patients [345].*

Figure 2: Diagnostic and treatment algorithm for men with acute epididymitis



i.m. = intramuscular; i.v. intravenously.
** Despite the lack of RCTs there is increasing evidence that intravenous treatment with ceftriaxone is safe and effective for the treatment of gonorrhoeal infections and avoids the discomfort of an intramuscular injection for patients [345].*

3.13 Fournier's Gangrene (Necrotising fasciitis of the perineum and external genitalia)

3.13.1 Epidemiology, Aetiology and Pathophysiology

Fournier's gangrene is an aggressive and frequently fatal polymicrobial soft tissue infection of the perineum, peri-anal region, and external genitalia [412]. It is an anatomical sub-category of necrotising fasciitis with which it shares a common aetiology and management pathway.

3.13.2 Diagnostic Evaluation

Typically, there is painful swelling of the scrotum or perineum with sepsis [412]. Examination shows small necrotic areas of skin with surrounding erythema and oedema. Crepitus on palpation and a foul-smelling exudate occurs with more advanced disease. Patient risk factors for occurrence and mortality include being immunocompromised, most commonly diabetes or malnutrition, recent urethral or perineal surgery, and high body mass index (BMI). In up to 40% of cases, the onset is more insidious with undiagnosed pain often resulting in delayed treatment [413]. A high index of suspicion and careful examination, particularly of obese patients, is required. Computed tomography or MRI can help define para-rectal involvement, suggesting the need for bowel diversion [412].

3.13.3 Disease Management

The degree of internal necrosis is usually vastly greater than suggested by external signs, and consequently, adequate, repeated surgical debridement with urinary diversion by suprapubic catheter is necessary to reduce mortality [412]. Consensus from case series suggests that surgical debridement should be early (< 24 hours) and complete, as delayed and/or inadequate surgery may result in higher mortality [412]. Immediate empiric parenteral antibiotic treatment should be given that covers all probable causative organisms and can penetrate inflammatory tissue. A suggested regime would comprise a broad-spectrum penicillin or third-generation cephalosporin, gentamicin and metronidazole or clindamycin [412]. This can then be refined, guided by microbiological culture.

3.13.4 Evidence Summary

A systematic literature search from 1980 to July 2017 was performed. From 640 references one RCT [414], two systematic reviews [415, 416], one narrative review [412], three registry studies [417-419], one prospective cohort study [420] and two retrospective comparative cohort studies with at least 25 patients [421, 422] were selected. The three registry studies from the United States [417-419], found mortality rates of 10%, 7.5% and 5% from 650, 1,641 and 9,249 cases, respectively. Older age, diabetes and high BMI were associated with higher risk. A prospective cohort study showed that disease-specific severity scores did predict outcome, but were not superior to generic scoring systems for critical care [420]. The evidence questions addressed were:

1. What is the best antimicrobial treatment strategy to reduce mortality?
2. What is the best debridement and reconstruction strategy to reduce mortality and aid recovery?
3. Are there any effective adjuvant treatments that improve outcome?

Concerning the evidence questions:

A. A low-quality retrospective case series [421] with 168 patients found no significant difference in mortality between patients given ≤ 10 days of parenteral antibiotics (80 patients) and those given > 10 days (88 patients).

B. A systematic review of wound closure techniques [416] found low-quality evidence from 16 case series involving 425 male patients. They recommended primary or secondary wound closure for scrotal defects ≤ 50% with the use of flaps or skin grafts for defects involving > 50% of the scrotum or with extension outside the scrotum.

C. A systematic review on the use of hyperbaric oxygen therapy [415] included three comparative case series and four other case series. All were retrospective and published prior to 2000. No consistent evidence of benefit was found; an RCT was advised. A more recent comparative case series [422] suggested benefit for use of hyperbaric oxygen therapy in 16 patients compared to 12 cases without use of such therapy in terms of reduced mortality and fewer debridements (low quality evidence). A low-quality RCT [414] with 30 patients found that use of honey-soaked dressings resulted in a shorter hospital stay (28 vs. 32 days) than dressing soaked with Edinburgh solution of lime (EUSOL). We found no evidence of benefit for use of negative-pressure (vacuum) wound therapy in Fournier's gangrene.

3.13.5 *Summary of evidence and recommendations for the disease management of Fournier's Gangrene*

Summary of evidence	LE
Immediate empiric parenteral antibiotic treatment should be given that covers all probable causative organisms and can penetrate inflammatory tissue.	3
A systematic review of wound closure techniques recommended primary or secondary wound closure for scrotal defects ≤ 50% with the use of flaps or skin grafts for defects involving > 50% of the scrotum or with extension outside the scrotum.	3
No consistent evidence of benefit for hyperbaric oxygen therapy was found.	3
A low quality RCT found that dressings soaked in honey resulted in a shorter hospital stay than dressing soaked with EUSOL.	3
No evidence of benefit for use of negative-pressure (vacuum) wound therapy in Fournier's gangrene was found.	4

Recommendations	Strength rating
Start treatment for Fournier's gangrene with broad-spectrum antibiotics on presentation, with subsequent refinement according to culture and clinical response.	Strong
Commence repeated surgical debridement for Fournier's gangrene within 24 hours of presentation.	Strong
Do not use adjunctive treatments for Fournier's gangrene except in the context of clinical trials.	Weak

Table 11: Suggested regimens for antimicrobial therapy for Fournier's Gangrene of mixed microbiological aetiology adapted from [423].

Antimicrobial	Dosage
Piperacillin-tazobactam plus Vancomycin	4.5 g every 6-8 h IV 15 mg/kg every 12 h
Imipenem-cilastatin	1 g every 6-8 h IV
Meropenem	1 g every 8 h IV
Ertapenem	1 g once daily
Gentamicin	5 mg/kg daily
Cefotaxime plus metronidazole or clindamycin	2 g every 6 h IV 500 mg every 6 h IV 600-900 mg every 8 h IV
Cefotaxime plus fosfomycin plus metronidazole	2 g every 6 h IV 5 g every 8 h IV 500 mg every 6 h IV

IV = intravenous.

3.14 Management of Human papillomavirus in men

3.14.1 *Epidemiology*

Human papilloma virus (HPV) is one of the most frequently sexually transmitted viruses encompassing both oncogenic (low- and high-risk variants) and non-oncogenic viruses. HPV 16 is the most common oncogenic variant, detected in 20% of all HPV cases [424]. A recent meta-analysis revealed a prevalence of 49% of any type of HPV and 35% of high-risk HPV in men [425]. Similar to the female genital tract, half of all HPV infections in the male genital tract are co-infections (≥ 2 HPV strains) [426].

HPV presence is dependent on study setting. In men attending urological clinics HPV was detected in 6% of urine samples [427]. A meta-analysis reported seminal HPV in 4.5-15.2% of patients resulting in seminal HPV being associated with decreased male fertility [424]. A cross sectional study of 430 men presenting for fertility treatment detected HPV in 14.9% of semen samples [428]. The presence of HPV in semen was not associated with impaired semen quality [428]. However, another systematic review reported a possible association between

HPV and altered semen parameters, and in women possible miscarriage or premature rupture of the membrane during pregnancy [429]. HPV6 and/or 11 were the most common genotypes detected in an observational study of anogenital warts, whilst HPV16 is correlated with severity of anal cytology [430]. The incidence of non-oncogenic HPV infection has been shown to be higher in men than women [431]. In males, approximately 33% of penile cancers and up to 90% of anal cancers are attributed to high-risk HPV infections, primarily with HPV16 [432]. The EAU Penial Cancer Guidelines will publish a comprehensive update in March 2022 including the results of two systematic reviews on HPV and penile cancer. Oral HPV is associated with oropharyngeal carcinomas approximately 22.4%, 4.4% and 3.5% of oral cavity, oropharynx and larynx cancers, respectively are attributed to HPV [432]. Systematic reviews have reported prevalence rates of oral HPV from 5.5-7.7%, with HPV16 present in 1-1.4% of patients [433, 434].

*3.14.2 **Risk factors***

Risk factors for HPV infection include early age of first sexual intercourse, sexual promiscuity, higher frequency of sexual intercourse, smoking and poor immune function [435-439]. Incidence and prevalence of overall HPV was considerably higher in MSM compared to heterosexuals [433, 436]. Overall, the prevalence of HPV in different sites seems to be higher in young, sexual-active adults compared to other population groups [435]. Stable sexual habits, circumcision and condom use are protective factors against HPV [425, 439-443]. Added risk factors of oral HPV infection are alcohol consumption, poor oral hygiene and sexual behaviours (oral and vaginal) [433, 435]. Positive HIV status, phimosis, and HPV status of the partner have also been associated with anogenital HPV status and decreased clearance in a number of studies [440].

*3.14.3 **Transmission***

HPV typically spreads by sustained direct skin-to-skin or mucosal contact, with vaginal, oral and anal sex being the most common transmission route [437]. In addition, HPV has been found on surfaces in medical settings and public environments raising the possibility of object-to-skin/mucosa transmission [444]. Further studies on non-sexual and non-penetrative sexual transmission are needed to understand the complexity of HPV transmission. HPV transmission may also be influenced by genotype, with a higher incidence of HPV51 and HPV52 and a high prevalence of HPV16 and HPV18 in the general and high-risk male population [437].

*3.14.4 **Clearance***

HPV time-to-clearance ranges from 1.3 to 42.1 months [445]. Clearance may be influenced by HPV genotype, patients' characteristics and affected body site [436, 440, 445]. HPV 16 has the highest incidence of high-risk HPV variants and has the lowest clearance across sites [440].

*3.14.5 **Diagnosis***

There is currently no approved test for HPV in men. Routine testing to check for HPV or HPV-related disease in men is not recommended. A physical examination to identify HPV lesions should be carried out. An acetic acid test to diagnose sub-clinical HPV lesions may be performed. If the diagnosis is uncertain or there is a suspicion of cancer a biopsy should be carried out. Intra-urethral condylomas are relatively uncommon and are usually limited to the distal urethral meatus [446, 447]. Urethrocystoscopy may be used to diagnose the presence of intra-urethral or bladder warts [447]; however, there is no high-level evidence for the use of invasive diagnostic tools for localisation of intra-urethral HPV. For detailed recommendations on the diagnosis of anogenital warts please refer to the IUSTI-European guideline for the management of anogenital warts [448].

*3.14.6 **Treatment of HPV related diseases***

Approximately 90% of HPV infections do not cause any problems and are cleared by the body within 2 years. However, treatment is required when HPV infection manifests as anogenital warts to prevent the transmission of HPV-associated anogenital infection and to minimise the discomfort caused to patients [448]. Of the treatment options available only surgical treatment has a primary clearance rate approaching 100%.

3.14.6.1 Treatments suitable for self-application

Patient-applied treatments include podophyllotoxin, salicylic acid, imiquimod, polyphenon E, 5-fluoracil and potassium hydroxide [448]. Imiquimod 5% cream showed a total clearance of external genital or perianal warts in 50% of immunocompetent patients [449] as well as in HIV positive patients successfully treated with highly active antiretroviral therapy [450]. A Cochrane review of published RCTs found imiquimod to be superior to placebo in achieving complete clearance of warts (RR: 4.03, 95% CI: 2.03–7.99) [451]. The recommended treatment schedule is imiquimod 5% cream applied to all external warts overnight 3 times each week for 16 weeks [448]. In an RCT involving 502 patients with genital and/or perianal warts sinecatechins 15% and 10% showed a complete clearance of all baseline and newly occurring warts in 57.2% and 56.3% of patients, respectively vs. 33.7% for placebo [452]. In addition, sinecatechins 10% has been shown to be associated with lower short-term recurrence rates when used as sequential therapy after laser CO2 ablative therapy [453].

Sinecatechins is applied three times daily until complete clearance, or for up to 16 weeks. Clearance rates of 36–83% for podophyllotoxin solution and 43–70% for podophyllotoxin cream have been reported [448]. A systematic review and meta-analysis confirmed the effectiveness of podophyllotoxin 0.5% solution relative to placebo (RR: 19.86, 95% CI: 3.88–101.65) [454]. Podophyllotoxin is self-applied to lesions twice daily for 3 days, followed by four rest days, for up to 4 or 5 weeks. An RCT has also shown potassium hydroxide 5% to be an effective, safe, and low-cost treatment modality for genital warts in men [455].

3.14.6.2 Physician-administered treatment

3.14.6.2 Physician-administered treatment

Physician-administered treatments included cryotherapy (79-88% clearance rate; 25-39% recurrence rate), surgical treatment (61-94% clearance rate), including excision, electrosurgery, electrocautery and laser therapy (75% clearance rate) [456, 457]. Physician-administered therapies are associated with close to 100% clearance rates, but they are also associated with high rates of recurrence as they often fail to eliminate invisible HPV-infected lesions [456, 457]. No data about the superiority of one treatment over another are available. However, among all interventions evaluated in a recent systematic review and network meta-analysis, surgical excision appeared to be the most effective treatment at minimising risk of recurrence [458].

3.14.6.3 Summary of evidence and recommendations for the treatment of anogenital warts

Summary of evidence	**LE**
A Cochrane review of published RCTs found imiquimod to be superior to placebo in achieving complete clearance of warts.	1b
In an RCT sinecatechins 15% and 10% showed a complete clearance of all baseline and newly occurring warts in 57.2% and 56.3% of patients, respectively vs. 33.7% for placebo	1b
A systematic review and meta-analysis confirmed the effectiveness of podophyllotoxin 0.5% solution relative to placebo	1b
A systematic review and meta-analysis reported that among all physician-applied therapy, surgical excision seemed to be the most effective at minimising risk of recurrence.	1a

Recommendations	**Strength rating**
Use self-administered imiquimod 5% cream applied to all external warts overnight 3 times each week for 16 weeks for the treatment of anogenital warts.	Strong
Use self-administered sinecatechins 15% or 10% applied to all external warts three times daily until complete clearance, or for up to 16 weeks for the treatment of anogenital warts.	Strong
Use self-administered podophyllotoxin 0.5% self-applied to lesions twice daily for 3 days, followed by four rest days, for up to 4 or 5 weeks for the treatment of anogenital warts.	Strong
Use cryotherapy or surgical treatment (excision, electrosurgery, electrocautery and laser therapy) to treat anogenital warts based on an informed discussion with the patient.	Strong

*3.14.7 **Circumcision for reduction of HPV prevalence***

Male circumcision is a simple surgical procedure which has been shown to reduce the incidence of sexually transmitted infections including HIV, syphilis and HSV-2 [459]. Two systematic reviews and meta-analyses, showed an inverse association between male circumcision and genital HPV prevalence in men [443, 445]. It has been suggested that male circumcision could be considered as an additional one-time preventative intervention likely to reduce the burden of HPV-related diseases in both men and women, particularly among those countries in which HPV vaccination programs and cervical screening are not available [445].

Summary of evidence	**LE**
Two systematic reviews and meta-analyses, showed an inverse association between male circumcision and genital HPV prevalence in men	1a

Recommendation	Strength rating
Discuss male circumcision with patients as an additional one-time preventative intervention for HPV-related diseases.	Strong

*3.14.8 **Therapeutic vaccination***

Three different vaccines against HPV have been licensed to date, but routine vaccination of males is currently implemented in only a few countries including Australia, Canada, the USA and Austria16. The aim of male vaccination is to reduce the rate of anal and penile cancers as well as head and neck cancers [432, 460].

A systematic review including a total of 5,294 patients reported vaccine efficacy against persisting (at least six months) anogenital HPV16 infections of 46.9% (28.6-60.8%) and against persisting oral infections of 88% (2–98%). A vaccine efficacy of 61.9% (21.4–82.8%) and 46.8% (20-77.9%) was observed against anal intraepithelial neoplasia grade 2 and 3 lesions, respectively [432]. The systematic review reported no meaningful estimates on vaccine efficacy against penile intraepithelial neoplasia grade 2 or 3, and no data were identified for anal, penile or head and neck squamous cell cancers [432].

A phase III clinical trial including 180 male patients evaluated the potential of MVA E2 recombinant vaccinia virus to treat intraepithelial lesions associated with papillomavirus infection [461]. the study showed promising results in terms of immune system stimulation against HPV lesions as well as regression in intraepithelial lesions.

Summary of evidence	LE
The role of therapeutic HPV vaccination in males in terms of effectiveness and safety is limited by the small number of relevant studies.	2
Therapeutic HPV vaccination in males is moderately effective against persistent anogenital HPV16 infection [(46.9% (28.6-60.8%)] and high-grade anal intraepithelial lesions [grade 2: 61.9% (21.4–82.8%); grade 3: 46.8% (20-77.9%)].	1b

Recommendation	Strength rating
Offer HPV vaccine to males after surgical removal of high-grade anal intraepithelial neoplasia.	Weak

*3.14.9 **Prophylactic vaccination***

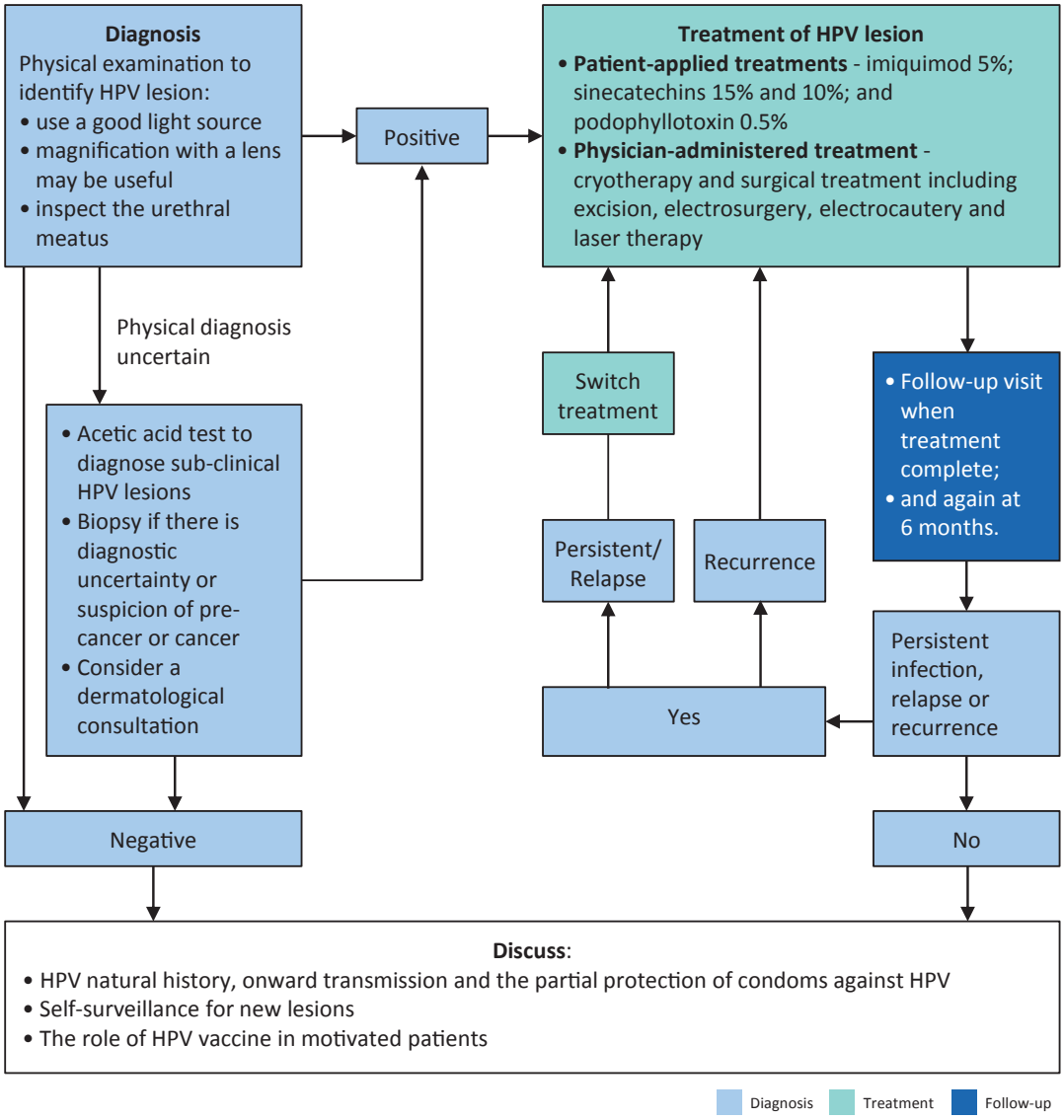
A systematic review and meta-analysis reported that vaccination is moderately effective against genital HPV-related diseases irrespective of an individual's HPV status; however, higher vaccine efficacy was observed in HPV-naïve males [432]. Supporting the early vaccination of boys with the goal of establishing optimal vaccine-induced protection before the onset of sexual activity [432]. An RCT including 1,124 demonstrated high efficacy of the quadrivalent HPV vaccine vs. placebo against HPV6/11/16/18-related persistent infections [462]. Furthermore, the vaccine elicited a robust immune response and was well tolerated with mild vaccination-related adverse events e.g. injection-site pain and swelling [462]. In addition, a Cochrane review, demonstrated that the quadrivalent HPV vaccine appears to be effective in the prevention of external genital lesions and genital warts in males [463].

Despite the fact quadrivalent HPV vaccines were approved for use in young adult males in 2010 vaccination rates have remained low at 10-15% [464]. Barriers to uptake in this patient group include lack of awareness about HPV vaccines and HPV-related diseases, concerns about vaccine safety and efficacy, economic/cost issues related to vaccine uptake, underestimation of HPV infection risks and sexual activity [464]. Health care professionals should provide easily understood and accessible communication resources regarding these issues, in order to educate young adult males and their families on the importance of HPV vaccination to reduce the incidence of certain cancers in the later life [464, 465].

Summary of evidence	LE
HPV vaccine is effective in the prevention of external genital lesions and genital warts in males.	1a
HPV vaccination is moderately effective against genital HPV-related diseases irrespective of a individual's HPV status; however, higher vaccine efficacy was observed in HPV-naïve males.	1a
A systematic review of HPV vaccination barriers among adolescent and young adult males identified a number of barriers to vaccine uptake including fear of side-effects, limited HPV awareness, financial costs and changes in sexual activity.	1b
An intervention study to evaluate whether electronic messaging can increase human papillomavirus vaccine completion and knowledge among college students concluded that intervention increased knowledge but not vaccine completion.	2b

Recommendations	Strength rating
Offer early HPV vaccination to boys with the goal of establishing optimal vaccine-induced protection before the onset of sexual activity.	Strong
Apply diverse communication strategies in order to improve HPV vaccination knowledge in young adult males.	Strong

Figure 3: Diagnostic and treatment algorithm for the management of HPV in men



3.15 Genitourinary Tuberculosis

*3.15.1 **Epidemiology, Aetiology and Pathophysiology***

An estimated 246,000 new and relapse tuberculosis (TB) cases occurred in the WHO European Region in 2019, with 49,752 of these cases occurring within the 31 countries comprising the European Union (EU)/European Economic Area (EEA) region [466]. An estimated 12.0% of incident TB cases in 2019 were co-infected with HIV. Extrapulmonary TB was notified on average for 16.6% of all incident TB cases in the Region. Eleven countries reported more than 30% of their TB cases having extrapulmonary localisation. The proportion of TB that is extrapulmonary is significantly greater among migrants than non-migrants. Genitourinary tuberculosis (GUTB) accounted for 4.6% of extrapulmonary TB cases in the EU between 1997-2017 [467]. Tuberculosis is an infectious disease caused by a group of *Mycobacterium* species called the *Mycobacterium tuberculosis* complex (MBTC) [468]. Genitourinary TB can affect all genitourinary organs and is almost always secondary due to the hematogenous spread of chronic latent TB infection (LTBI) [469]. Risk factors include primary and LTBI, diabetes, old age, low BMI, oncological comorbidities, immune suppression (including HIV), renal failure and poor socioeconomic living conditions. The risk of reactivation is estimated to be up to 15% during one's lifetime [470]. The WHO recommend either a tuberculin skin test (TST) or interferon-gamma release assay (IGRA) for the diagnosis LTBI [471].

*3.15.2 **Diagnosis***

The diagnosis of GUTB is challenging as no single diagnostic test exists. Diagnosis relies on a high suspicion of infection based on patient history; microbiological, molecular and histological testing; and imaging findings. Patients generally present with non-specific urological complaints for which no obvious cause is identified including haematuria, increased urinary frequency, difficulty voiding, abdominal, lumbar and suprapubic pain, and in female patients menstrual irregularities and pelvic pain. Patients may also present for infertility issues; however, infertility and TB will not be addressed in detail in this text.

3.15.2.1 Smear Microscopy

Smear microscopy is a simple and cost-effective way of detecting the presence of acid-fast bacilli (AFB) in urine samples, semen, tissue specimens, pus, or discharged or prostatic massage fluid, through microscopic examination using Ziehl–Neelsen or auramine staining [472, 473]. A major limitation of smear microscopy is its low sensitivity (ranging from 0-25%) in urine [474, 475].

3.15.2.2 Culture

The culture-based method (both solid and liquid media) for biological specimens is the reference standard for *M. tuberculosis* isolation from biological samples. Three midstream first-void urine samples, on consecutive days, are recommended for TB culture [473]. A disadvantage of culture-based methods is the long incubation period needed for results at least 9–10 days for positive results and 6 weeks to be considered negative as well as the need for highly equipped laboratories. In addition, studies have reported high specificities of 92–100% but low sensitivities 23.3–30% for urine culture in renal TB specimens [476, 477].

3.15.2.3 Nucleic Acid Amplification Tests

In recent years, nucleic acid amplification tests (NAATs) have been introduced in the diagnostic pathway of TB, to overcome the limits of early and rapid diagnosis and of drug susceptibility testing. In 2021 the WHO issued an update to its guidelines for the rapid diagnosis of TB in which they made a conditional recommendation that in patients with signs and symptoms of extrapulmonary TB, Xpert MTB/RIF may be used as an the initial diagnostic test [478]. Xpert MTB/RIF pooled sensitivity and specificity were 84.7% (70.8 to 93.1) and 97.3% (91.0 to 99.2) for the diagnosis of genitourinary TB [479]. The 2021 WHO guidelines also contain a number a recommendations for additional PCR testing systems as well as moderate complexity automated NAATs [478].

Note: A number of other diagnostic tests are currently under investigation by the WHO but cannot be recommended for the diagnosis of GUTB at this time.

3.15.2.4 Imaging

Imaging modalities aid in the localisation of the foci of infection in GUTB and in the assessment of the extent of the damage to the genito-urinary system. Imaging techniques for the diagnosis of GUTB have a sensitivity of approx. 90% [480]. However, the quality of the evidence available for diagnostic imaging of TB is low to very-low and further studies are required to allow the Panel to make recommendations on this topic.

Ultrasound is a cost-effective and non-invasive imaging modality that has been shown to be effective for the diagnosis of testicular, epididymal and vas deferens TB [481-485]. Ultrasound examination may also allow for the identification of parenchymal masses, cavities, mucosal thickening of the collecting system and bladder, stenosis and consecutive obstruction of the collecting system, vesicoureteral reflux, and calcifications [486]. In female GUTB patients US may identify ovarian masses, intrauterine thickening and calcifications [487].

Intravenous urography aids in the identification of renal and ureteral TB, but lacks specificity. Approximately 10-15% of patients may have normal findings on IVU [488, 489]. The most common findings on IVU are hydrocalycosis, hydronephrosis or hydroureter due to stricture, autonephrectomy and urinary calcifications [490-492].

In recent years CT and MRI have largely replaced IUV. The most common findings on CT are parenchymal scarring, hydrocalycosis, hydronephrosis or hydroureter due to stricture, and thickening of the renal pelvis, ureter and bladder walls [490-492]. In TB of the seminal vesicles and vas deferens CT imaging can show enlarged heterogeneously enhancing seminal vesicles with possible wall thickening, contraction, and intraluminal or wall calcifications [493, 494]. Prostate TB appears as a low attenuating and marginally enhancing cystic mass, which is indistinguishable from a non-TB prostatic abscess [495]. In female GUTB the fallopian tubes are most frequently affected area and present with enlargement, hydrosalpinx, pyosalpinx, and wall thickening, with calcification on CT [496].

Magnetic resonance imaging has low sensitivity for the diagnosis of GUTB in the early stages of the infection [497]. As an imaging modality MRI is useful in patients in whom CT is contraindicated, including patients with renal failure or contrast hypersensitivity reactions or those who wish to avoid exposure to radiation. Renal and ureteral abnormalities are comparable to those described for CT findings and must be distinguished from acute pyelonephritis [487, 498]. Epididymitis and testicular TB appears as a diffusely enlarged epididymis or testis with heterogeneous high T2 signal due to fibrosis and calcification [494]. Multiparametric MRI of the prostate distinguishes between the nodular or diffuse patterns of prostate TB [499].

Female GUTB has a wide range of appearances on HSG affecting the fallopian tubes, endometrium and uterus [500, 501]. Tubal obstruction is the most common finding with HSG [501]. In addition, deformity of the uterine cavity can be observed, such as a T-shaped and Dwarfed uterus, resulting from abnormal scaring and fibrosis [500]. As the disease progresses this process can potentially lead to a complete obliteration of the uterine cavity referred to as Netter syndrome [502].

*3.15.3 **Medical Treatment***

The WHO recommends a daily six month regimen for treatment of newly diagnosed extrapulmonary TB, including an intensive phase of two months with isoniazid, rifampicin, pyrazinamide, and ethambutol, followed by a continuation phase of four months with isoniazid and rifampicin [503]. For the treatment of multi-drug resistant (MDR) TB (i.e. resistance to rifampicin and isoniazid) an individualised treatment regime should be applied with at least five effective tuberculosis medicines during the intensive phase, including pyrazinamide and four core second-line tuberculosis medicines [504].

*3.15.4 **Surgical treatment***

Combination drug therapy is the first-line treatment for GUTB. However, in more than 50% of patients ablative, endoscopic or reconstructive surgery is required due to the destructive nature of the infection coupled with a delay in initial diagnosis [505-507]. In 26.9% of cases of diagnosed GUTB there is a non-functioning unilateral kidney and in 7.4%, renal failure [507].

In the largest observational study of 4,288 GUTB patient's a total of 2,364 different surgical procedures were carried out of which 948 were reconstructive [508]. In a retrospective series of 241 patients who underwent surgery for GUTB, a total of 128 reconstructive procedures were done in which 30.29% of patients had bladder augmentation [509]. A retrospective single-centre study of 128 patients reported renal units in the reconstruction group had 5.44-fold longer survival than the permanent diversion group suggesting that when feasible renal reconstruction may be better for renal function preservation [510]. Reconstructive surgery may include augmentation cystoplasty, uretero-ureterostomy, ureteroneocystostomy, ureteral reimplant, pyeloplasty, ureterocalicostomy and ileal ureter or external diversion, where indicated [511].

There is limited evidence with regard to the optimum surgical approach. Minimally invasive options, have been reported as feasible and safe strategies, comparable to open surgery [512-516]. In addition, the optimal timing for surgery is controversial. A delay of 2-6 weeks up to 9 months after the initiation of medical treatment has been proposed to allow for a reduction in active inflammation and stabilisation of the TB lesions [497].

Due to lack of high-quality evidence for surgical treatment of GUTB the Panel are unable to give a recommendation on surgical treatment at this point in time. Patients with GUTB should be assessed on an individualised bases and the decision to operate taken depending on the location, extent of disease progression and damage to the genitourinary system.

3.15.5 *Summary of evidence and recommendations for the diagnosis and treatment of GUTB*

Summary of evidence	LE
The risk of reactivation of latent TB is estimated to be 15% in an individual's lifetime.	2a
Smear microscopy for acid-fast bacilli has a low sensitivity in urine ranging from 0-25%.	2a
Studies have reported high specificities of 92–100% but low sensitivities of 23.3–30% for urine culture in renal TB specimens.	2a
Xpert MTB/RIF pooled sensitivity and specificity were 84.7% (70.8 to 93.1) and 97.3% (91.0 to 99.2) for the diagnosis of GUTB.	1b
Standard six month anti-tuberculous drug regimens are effective in all forms of TB (pulmonary and extrapulmonary).	1a
There is limited evidence with regard to the optimum surgical approach and timing of surgery in GUTB patients.	3

Recommendations	Strength rating
Diagnosis	
Take a full medical history including history of previous tuberculosis infection (pulmonary and extrapulmonary) form all patients presenting with persistent non-specific genitourinary symptoms and no identifiable cause.	Strong
Perform smear microscopy on urine, semen, tissue specimens, discharged or prostatic massage fluid using Ziehl–Neelsen (ZN) or auramine staining in patients with suspected genitourinary tuberculosis (GUTB).	Weak
Perform acid-fact bacilli culture on three midstream first-void urine samples, on three consecutive days for M. tuberculosis isolation in patients with suspected GUTB.	Strong
Use a recommended PCR test systems in addition to microbiological reference standard (MRS) in urine specimens as a diagnostic test in patients with signs and symptoms of GUTB.	Weak
Use imaging modalities in combination with culture and/or PCR to aid in the diagnosis of GUTB and to assess the location and extent of damage to the genitourinary system.	Weak
Treatment	
Use medical treatment as first-line treatment for GUTB.	Strong
Use a daily six-month regimen for treatment of newly diagnosed GUTB this should include an intensive phase of two months with isoniazid, rifampicin, pyrazinamide and ethambutol. Followed by a continuation phase of four-months with isoniazid and rifampicin.	Strong
Treat multi-drug resistant TB with an individualised treatment regime including at least five effective tuberculosis medicines during the intensive phase, including pyrazinamide and four core second-line tuberculosis medicines.	Strong

Table 12: Treatment regimens for newly diagnosed GUTB and MDR-TB [504]

Antimicrobials	Dosage
Six month regimen for treatment of newly diagnosed GUTB	
Intensive two month phase	
Isoniazid	5 mg/kg every 24 h; max daily dosage 300 mg
Rifampicin	10 mg/kg every 24 h; max daily dosage 600 mg
Pyrazinamide	25 mg/kg every 24 h; max daily dosage 2000 mg
Ethambutol	15–20 mg/kg every 24 h; max daily dosage ranging from 800 mg to 1600 mg depending on body weight
Continuation four month phase	
Isoniazid	5 mg/kg every 24 h; max daily dosage 300 mg
Rifampicin	10 mg/kg every 24 h; max daily dosage 600 mg

Treatment regimen for multi-drug resistant TB	
Treat multi-drug resistant TB with an individualised treatment regime including at least five effective tuberculosis medicines during the intensive phase, including pyrazinamide and four core second-line tuberculosis medicines*.	
Group A Fluoroquinolones	Levofloxacin, Moxifloxacin and Gatifloxacin
Group B Second-line injectables	Amikacin, Capreomycin, Kanamycin and Streptomycin**
Group C Other second-line agents	Ethionamide/ Prothionamide, Cycloserine/Terizidone, Linezolid and Clofazimine
Group D Add-on agents (not part of the core MDR-TB regime)	D1: Pyrazinamide, Ethambutol, and High-dose isoniazid D2: Bedaquiline and Delamamid D3: p-aminosalicylic acid, Imipenem-cilastatin, Meropenem, Amoxicillin-clavulanate and Thioacetazone***

** Drugs should be chosen as follows: 1 from group A, 1 from group B, and at least 2 from group C. If the minimum number of five TB medicines cannot be composed from drugs included in Groups A to C, an agent from group D2 and other agents from group D3 may be added to bring the total to five [504].*

***Streptomycin can substitute other injectable drugs if none of these agents can be used and if the strain is shown not to be resistant [504].*

****Thioacetazone should not be used if the patient is HIV seropositive [504].*

3.16 Peri-Procedural Antibiotic Prophylaxis

*3.16.1 **General Principles***

3.16.1.1 Definition of infectious complications

The European Centre for Disease Prevention and Control (ECDC) and the CDC have both presented similar definitions recommended for the evaluation of infectious complications [517, 518].

3.16.1.2 Non-antibiotic measures for asepsis

There are a number of non-antibiotic measures designed to reduce the risk of surgical site infection (SSI), many are historically part of the routine of surgery. The effectiveness of measures tested by RCTs are summarised in systematic reviews conducted by the Cochrane Wounds Group (http://wounds.cochrane.org/news/reviews). Urological surgeons and the institutions in which they work should consider and monitor maintenance of an aseptic environment to reduce risk of infection from pathogens within patients (microbiome) and from outside the patient (nosocomial/healthcare-associated). This should include use of correct methods of instrument cleaning and sterilisation, frequent and thorough cleaning of operating rooms and recovery areas and thorough disinfection of any contamination. The surgical team should prepare to perform surgery by effective hand washing [519], donning of appropriate protective clothing and maintenance of asepsis. These measures should continue as required in recovery and ward areas.

Patients should be encouraged to shower pre-operatively, but use of chlorhexidine soap does not appear to be beneficial [520]. Although evidence quality is low, any required hair removal appears best done by clipping, rather than shaving, just prior to incision [521]. Mechanical bowel preparation should not be used as evidence review suggests harm not benefit [522, 523]. There is some weak evidence that skin preparation using alcoholic solutions or chlorhexidine result in a lower rate of SSI than iodine solutions [524]. Studies on the use of plastic adherent drapes showed no evidence of benefit in reducing SSI [525].

3.16.1.3 Detection of bacteriuria prior to urological procedures

Identifying bacteriuria prior to diagnostic and therapeutic procedures aims to reduce the risk of infectious complications by controlling any pre-operative detected bacteriuria and to optimise antimicrobial coverage in conjunction with the procedure. A systematic review of the evidence identified eighteen studies comparing the diagnostic accuracy of different index tests (dipstick, automated microscopy, dipslide culture and flow cytometry), with urine culture as the reference standard [526]. The systematic review concluded that none of the alternative urinary investigations for the diagnosis of bacteriuria in adult patients prior to urological interventions can currently be recommended as an alternative to urine culture [526].

3.16.1.4 Choice of agent

Urologists should have knowledge of local pathogen prevalence for each type of procedure, their antibiotic susceptibility profiles and virulence in order to establish written local guidelines. These guidelines should cover the five modalities identified by the ECDC following a systematic review of the literature [527]. The agent

should ideally not be one that may be required for treatment of infection. When risk of skin wound infection is low or absent, an aminoglycoside (gentamicin) should provide cover against likely uropathogens provided the eGFR is > 20 mL/min; second generation cephalosporins are an alternative [528]. Recent urine culture results including presence of any multi-resistant organisms, drug allergy, history of *C. difficile* associated diarrhoea, recent antibiotic exposure, evidence of symptomatic infection pre-procedure and serum creatinine should be checked. The panel have decided not to make recommendations for specific agents for particular procedures as there is considerable variation in Europe and worldwide regarding bacterial pathogens, their susceptibility and availability of antibiotic agents.

*3.16.2 **Specific procedures and evidence question***

An updated literature search from February 2017 (cut-off of last update) to June 2021 identified RCTs, systematic reviews and meta-analyses that investigated the benefits and harms of using antibiotic prophylaxis prior to specific urological procedures. The available evidence enabled the panel to make recommendations concerning urodynamics, cystoscopy, stone procedures (extracorporeal shockwave lithotripsy [ESWL], ureteroscopy and percutaneous nephrolithotomy [PCNL]), transurethral resection of the prostate (TURP) and transurethral resection of the bladder (TURB). For nephrectomy and prostatectomy the scientific evidence was too weak to allow the panel to make recommendations either for or against antibiotic prophylaxis. The general evidence question was: Does antibiotic prophylaxis reduce the rate of post-operative symptomatic UTI in patients undergoing each named procedure?

3.16.2.1 Urodynamics

The literature search identified one systematic review for antibiotic prophylaxis in women only [529]. This included 3 RCTs (n=325 patients) with the authors reporting that prophylactic antibiotics reduced the risk of bacteriuria but not clinical UTI after urodynamics [529]. A previous Cochrane review identified nine RCTs enrolling 973 patients with overall low quality and high or unclear risks of bias [530]. The outcome of clinical UTI was reported in four trials with no benefit found for antibiotic prophylaxis vs. placebo [RR (95%CI) 0.73 (0.52-1.03)]. A meta-analysis of nine trials showed that use of antibiotics reduced the rate of post-procedural bacteriuria [RR (95%CI) 0.35 (0.22-0.56)] [530].

3.16.2.2 Cystoscopy

Three systematic reviews and meta-analyses [531-533] and one additional RCT [534] on cystoscopy for stent removal were identified. Garcia-Perdomo *et al.*, included seven RCTs with a total of 3,038 participants. The outcome of symptomatic UTI was measured by five trials of moderate overall quality and meta-analysis showed a benefit for using antibiotic prophylaxis [RR (95%CI) 0.53 (0.31 – 0.90)]; ARR 1.3% (from 2.8% to 1.5%) with a NNT of 74 [532]. This benefit was not seen if only the two trials with low risk of bias were used in the meta-analysis. Carey *et al.*, included seven RCTs with 5,107 participants. Six trials were included in meta-analysis of the outcome of symptomatic bacteriuria which found benefit for use of antibiotic prophylaxis [RR (95%CI) 0.34 (0.27 – 0.47)]; ARR 3.4% (from 6% to 2.6%) with NNT of 28 [531]. Zeng *et al.*, included twenty RCTs and two quasi-RCTs with a total of 7,711 participants. The outcome of symptomatic UTI was measured by eleven RCTs of low overall quality and meta-analysis showed a possible benefit for using antibiotic prophylaxis [RR (95% CI) 0.49 (0.28 – 0.86)] [533]. For systemic UTI, antibiotic prophylaxis showed no effect compared with placebo or no treatment in five RCTs [RR (95% CI) 1.12 (0.38 - 3.32)]. However, prophylactic antibiotics may increase bacterial resistance [(RR (95% CI) 1.73 (1.04 – 2.87)].

Given the low absolute risk of post-procedural UTI in well-resourced countries, the high number of procedures being performed, and the high risk of contributing to increasing antimicrobial resistance the panel consensus was to strongly recommend not to use antibiotic prophylaxis in patients undergoing urethrocystoscopy (flexible or rigid).

3.16.2.3 Interventions for urinary stone treatment

3.16.2.3.1 Extracorporeal shockwave lithotripsy

For patients without bacteriuria undergoing ESWL two systematic reviews and meta-analyses were identified with latest search dates of November 2011 and October 2012, respectively [535, 536] and two further trials [537]. Lu *et al.*, included nine RCTs with a total of 1,364 patients and found no evidence of benefit in terms of reducing the rate of post-procedural fever or bacteriuria [535]. Mrkobrada *et al.*, included eight RCTs with a total of 940 participants and found no evidence of benefit for antibiotic prophylaxis to reduce rate of fever or trial-defined infection [536]. A RCT with 274 patients and severe risk of bias found no reduction in fever at up to one week post-procedure using a single dose of levofloxacin 500 mg and no difference in the rate of bacteriuria [537]. Another RCT (n=600) again with severe risk of bias found no difference in UTI and positive urine culture rates at two weeks post-procedure using 200 mg ofloxacin post-operatively for 3-days vs. placebo [538].

For patients with bacteriuria or deemed at high risk of complications one RCT comparing the use of ofloxacin or trimethoprim-sulphamethoxazole for three days prior and four days subsequent to ESWL in 56 patients with ureteric stents was identified [539]. They found no difference in rate of clinical UTI at seven days (no events) and no difference in post-ESWL bacteriuria.

3.16.2.3.2 Ureteroscopy

One updated systematic review and meta-analysis with last search date of June 2017 was identified and included eleven RCTs with 4,591 patients [540]. The meta-analysis found that post-operative pyuria and bacteriuria rates were significantly lower in patients who received pre-operative antibiotic prophylaxis pyuria (OR: 0.42, 95% CI 0.25–0.69 and OR: 0.25, 95% CI 0.11–0.58, respectively). Five studies assessed post-operative febrile UTI (fUTI) and found no difference in the rate of fUTIs between patients who did or did not receive antibiotic prophylaxis (OR: 0.82, 95% CI 0.40– 1.67; p=0.59). However, a significantly higher risk of post-operative fever in the pre-operative antibiotic prophylaxis group (OR: 1.75, 95% CI 1.22–2.50; p=0.002) was reported. A subgroup analysis on the type of pre-operative antibiotic prophylaxis found no difference between a single dose of oral vs. intravenous antibiotics [540].

A RCT comparing different ciprofloxacin-based antibiotic prophylaxis regimens on the incidence of SIRS after URS found there was no difference in the incidences of SIRS between the regimens including the zero-dose regime [541]. However, there was a greater risk of SIRS in patients who did not receive antibiotic prophylaxis when the stone size was > 200 mm^2 [541]. Another RCT comparing the use of two oral doses of 3g Fosfomycin tromethamine before surgery to standard of care did not find any difference in the incidence of infections, bacteriuria or fever [542].

Panel discussion considered that despite low quality evidence suggesting no benefit in reducing risk of clinical UTI, clinicians and patients would prefer to use prophylaxis to prevent kidney infection or sepsis. Ideally this should be examined in a robustly designed clinical study.

3.16.2.3.3 Percutaneous neprolithotomy (PNL)

The largest systematic review and meta-analysis performed, latest search date April 2019, included 1,549 patients in thirteen comparative studies on antibiotic prophylaxis strategies for PNL [543]. Compared with a single dose before surgery pre-operative antibiotic prophylaxis significantly reduced post-operative sepsis and fever (OR 0.31, 95%CI 0.20-0.50 and OR 0.26, 95%CI 0.14-0.48, respectively) [543]. Similarly, the rate of positive pelvic urine and positive stones culture were reduced when pre-operative prophylaxis was given. There was no difference in sepsis rates between patients receiving or not receiving post-operative prophylaxis; however, patients who received post-operative antibiotic prophylaxis had more fever [543].

Four RCTs with overall low risk of bias comparing different antibiotic regimes in PNL were identified [544-547]. Seyrek *et al.*, compared the rate of SIRS following PNL in 191 patients receiving either a combination of sulbactam/ampicillin or cefuroxime. There was no difference in SIRS or urosepsis rates [544]. Tuzel *et al.*, investigated single dose ceftriaxone versus ceftriaxone and subsequently an oral third-generation cephalosporin until after nephrostomy catheter withdrawal at mean (SD) of 3 (1) days in 73 participants undergoing PNL. They found no difference in rate of infectious complications between the two antibiotic regimens [545]. Taken *et al.*, compared the administration of 1g ceftriaxone and 1g cefazoline both administered 30 minutes before surgery and continued till nephrostomy removal. They found no difference in terms of SRIS or sepsis between groups [547]. Omar *et al.*, compared ciprofloxacin 200 mg IV vs. 2 mg cefotaxime 30 minutes before and 12hours after surgery and found a higher rate of fever in the cefotaxime group [546]. However, these results remain limited by the high risk of bias and the lack of data regarding post-operative infection. These studies give moderate evidence that a single dose of a suitable agent was adequate for prophylaxis against clinical infection after PNL.

3.16.2.4 Transurethral resection of the prostate

A systematic review of 39 RCTs with search date up to 2009 was identified [548]. The update search to February 2017 did not reveal any further relevant studies. Of the 39 RCTs reviewed by Dahm *et al.*, six trials involving 1,666 men addressed the risk of septic episodes, 17 trials reported procedure related fever and 39 investigated bacteriuria. Use of prophylactic antibiotics compared to placebo showed a relative risk reduction (95% CI) for septic episode of 0.51 (0.27-0.96) with ARR of 2% (3.4% - 1.4%) and a NNT of 50. The risk reduction (95% CI) for fever was 0.64 (0.55-0.75) and 0.37 (0.32-0.41) for bacteriuria.

3.16.2.5 Transurethral resection of the bladder

One systematic review which included seven trials with a total of 1,725 participants was identified [549]. Antimicrobial prophylaxis showed no significant effect on post-operative UTIs [OR (95% CI) 1.55 (0.73 - 3.31)] and asymptomatic bacteriuria [OR (95% CI) 0.43 (0.18 – 1.04)] [549]. The review did not attempt sub-group analysis according to presence of risk factors for post-operative infection such as tumour size. Risk factors for development of post-operative UTIs were evaluated only by three of the included studies and most of the parameters were analysed by no more than one study.

A RCT (n=100) comparing oral fosfomycin 3g (the night before surgery) vs. intravenous cefoxitin 2g (30 min pre- and 24 hrs post-surgery) on post-operative UTIs found that a single oral administration of fosfomycin was non-inferior to intravenous administration of cefoxitin in the prevention of post-TURB UTI, even in patients considered at higher risk [550].

Panel discussion concluded that a weak recommendation to use antibiotic prophylaxis for patients undergoing TURB who had a high risk of suffering post-operative sepsis would be appropriate.

3.16.2.6 Midurethral slings

One systematic review and meta-analysis identified one study assessing the role of pre-operative antibiotics for midurethral sling surgery alone [551]. The study was halted due to low rate of infectious outcomes seen at the first scheduled interim analysis. The study enrolled 29 women in the antibiotic prophylaxis (cefazolin) group and 30 in the placebo group with a total follow-up of six months. No statistically significant difference between the cefazolin and placebo groups, with respect to wound infections [1 (3.3%) and 0 (0%)] or bacteriuria [3 (10%) and 1 (3.5%)] was found [551].

3.16.2.7 Renal tumour ablation

One systematic review publication date 2018 included 6,952 patients across 51 studies [552]. Infectious complications were reported in 74 patients including fever (60.8%), abscess (21.6%) and UTI (8.1%). Prophylactic antibiotic use was reported in 5.4% of patients but it was not possible to study its association to infectious complications due to lack of reporting.

3.16.2.8 Prostate biopsy

3.16.2.8.1 Transperineal prostate biopsy

A total of eight randomised studies including 1,596 patients compared the impact of biopsy route on infectious complications. Infectious complications were significantly higher following transrectal biopsy (48 events among 789 men) compared to transperineal biopsy (22 events among 807 men), [RR (95% CIs) 2.48 (1.47 to 4.2) [553, 554]. In addition, a systematic review including 165 studies with 162,577 patients described sepsis rates of 0.1% and 0.9% for transperineal and transrectal biopsies, respectively [555]. Finally, a population-based study from the UK (n=73,630) showed lower re-admission rates for sepsis in patients who had transperineal versus transrectal biopsies (1.0% vs, 1.4%, respectively) [556]. The available evidence demonstrates that the transrectal approach should be abandoned in favour of the transperineal approach despite any possible logistical challenges.

A systematic review and meta-analysis of eight non-RCTs reported no significant differences between patients receiving or not receiving antibiotic prophylaxis in terms of post-biopsy infection (0.11% vs. 0.31%) and sepsis (0.13% vs. 0.09%), for the transperineal approach [557]. This is in line with another systematic review and meta-analysis of 112 individual patient cohorts which also showed no significant difference in the number of patients experiencing post-transperineal biopsy infection with 1.35% of 29,880 patients receiving antibiotic prophylaxis and 1.22% of 4,772 not receiving antibiotic prophylaxis (p=0.8) [558]. In addition, two recently published RCTs have reported comparably low post-biopsy infection rates for transperineal biopsy regardless of whether antibiotic prophylaxis was administered or not [559, 560].

There is a growing body of evidence to suggest that antibiotic prophylaxis may not be required for transperineal biopsy; however, the Panel have chosen to wait until a number of ongoing RCTs report their study findings before making a recommendation on this.

3.16.2.8.2 Transrectal prostate biopsy

An updated meta-analysis of eleven RCTs including 2,237 men showed that use of a rectal povidone-iodine preparation before biopsy, in addition to antimicrobial prophylaxis, resulted in a significantly lower rate of infectious complications [RR (95% CIs) 0.47 (0.36 to 0.61) [553, 561-563]. Single RCTs showed no evidence of benefit for perineal skin disinfection [564], but reported an advantage for rectal povidone-iodine preparation before biopsy compared to after biopsy [565].

A meta-analysis of four RCTs including 671 men evaluated the use of rectal preparation by enema before transrectal biopsy. No significant advantage was found regarding infectious complications [RR (95% CIs) 0.96 (0.64 to 1.54) [553].

An updated meta-analysis of 29 RCTs with 4,127 patients found no evidence that use of peri-prostatic injection of local anaesthesia resulted in more infectious complications than no injection [RR (95% CIs) 1.08 (0.80 to 1.49)] [553, 554, 566, 567]. An updated meta-analysis of 10 RCTs including 2,342 patients found that extended biopsy templates showed comparable infectious complications to standard templates [RR (95% CIs) 0.82 (0.55 to 1.24)] [553, 568]. Additional meta-analyses found no difference in infections complications regarding needle guide type (disposable vs. reusable), needle type (coaxial vs. non-coaxial), needle size (large vs. small), and number of injections for peri-prostatic nerve block (standard vs. extended) [553].

A meta-analysis of eleven studies with 1,753 patients showed significantly reduced infections after transrectal prostate biopsy when using antimicrobial prophylaxis as compared to placebo/control [RR (95% CIs) 0.56 (0.40 to 0.77)] [569].

Fluoroquinolones have been traditionally used for antibiotic prophylaxis in this setting; however, overuse and misuse of fluoroquinolones has resulted in an increase in fluoroquinolone resistance. In addition, the European Commission has implemented stringent regulatory conditions regarding the use of fluoroquinolones resulting in the suspension of the indication for peri-operative antibiotic prophylaxis including prostate biopsy [138].

A systematic review and meta-analysis on antibiotic prophylaxis for the prevention of infectious complications following prostate biopsy concluded that in countries where fluoroquinolones are allowed as antibiotic prophylaxis, a minimum of a full one-day administration is recommended [569]. An updated meta-analysis of eight RCTs with 2,939 patients confirmed that targeted therapy (antibiotic guidance based on rectal swab microbiology) in case of fluoroquinolone resistance is associated with reduced infectious complications [RR (95% CIs) 0.54 (0.40 to 0.72)] [569]. In addition, an updated meta-analysis of ten RCTs with 2,787 patients comparing augmented prophylaxis (combination of two or more different classes of antibiotics) to standard prophylaxis showed augmented prophylaxis to be superior [RR (95% CIs) 0.44 (0.32 to 0.59)] [569, 570]. In countries where use of fluoroquinolones are suspended cephalosporins or aminoglycosides can be used as individual agents with comparable infectious complications based on meta-analysis of two RCTs [569]. An updated meta-analysis of four RCTs compared fosfomycin trometamol to fluoroquinolones [RR (95% CIs) 0.62 (0.37 to 1.06)] [569, 571]. Although initial RCTs suggested fosfomycin trometamol to be superior the latest Swedish study, which aimed to recruit 3,448 patients, was discontinued after 42 patients due to the unusually high number of hospitalisations in the fosfomycin trometamol group [571]. Therefore, routine general use should be critically assessed due to the relevant infectious complications also reported in non-randomised studies [572]. Of note the indication of fosfomycin trometamol for prostate biopsy has been withdrawn in Germany as the manufacturers did not submit the necessary pharmacokinetic data in support of this indication. Urologists are advised to check their local guidance in relation to the use of fosfomycin trometamol for prostate biopsy. Another possibility is the use of augmented prophylaxis without fluoroquinolones, although no standard combination has been established to date. Finally, targeted prophylaxis based on rectal swap/stool culture is plausible, but no RCTs are available on non-fluoroquinolones. See figure 1 for prostate biopsy workflow to reduce infections complications.

3.16.3 Summary of evidence and recommendations for peri-procedural antibiotic prophylaxis

Summary of evidence	**LE**
The outcome of clinical UTI was reported in four out of eleven RCTs with no benefit found for antibiotic prophylaxis vs. placebo in patients following filling and voiding cystometry.	1b
A meta-analysis of five trials of moderate quality showed a benefit for using antibiotic prophylaxis for the reduction of symptomatic UTI in patients undergoing cystoscopy. However, this benefit was not seen if only the two trials with low risk of bias were used in the meta-analysis.	1a
Two meta-analyses found no benefit for antibiotic prophylaxis following ESWL in terms of reducing the rate of post-procedural fever and bacteriuria or trial-defined infection in patients without bacteriuria.	1a
Two meta-analyses found no evidence of benefit for antibiotic prophylaxis prior to ureteroscopy in reducing the rate of clinical UTI; however, the rate of bacteriuria was reduced.	1a
A meta-analysis of five RCTs demonstrated a moderate level of evidence that antibiotic prophylaxis was associated with a statistically significant reduction in the risk of post-procedural UTI following PNL.	1a
Two RCTs concluded that a single dose of a suitable agent was adequate for prophylaxis against clinical infection after PNL.	1b

A systematic review of 39 RCTs concluded that antibiotic prophylaxis reduced the rate of infectious complications in men undergoing TURP.	1b
A systematic review of two RCTs found no benefit for antibiotic prophylaxis in patients undergoing TURB.	1b
A meta-analysis of eight studies including 1,596 patients showed significantly reduced infectious complications in patients undergoing transperineal biopsy as compared to transrectal biopsy.	1a
A meta-analysis of eight non-RCTS reported comparable rates of post-biopsy infections in patients undergoing transperineal biopsy irrespective if antibiotic prophylaxis was given or not.	1a
A meta-analysis of eleven RCTs including 2,237 men showed that use of a rectal povidone-iodine preparation before transrectal biopsy, in addition to antimicrobial prophylaxis, resulted in a significantly lower rate of infectious complications.	1a
A meta-analysis on eleven studies with 1,753 patients showed significantly reduced infections after transrectal biopsy when using antimicrobial prophylaxis as compared to placebo/control.	1a

Recommendations	**Strength rating**
Do not use antibiotic prophylaxis to reduce the rate of symptomatic urinary infection following: • urodynamics; • cystoscopy; • extracorporeal shockwave lithotripsy.	Strong
Use antibiotic prophylaxis to reduce the rate of symptomatic urinary infection following ureteroscopy.	Weak
Use single dose antibiotic prophylaxis to reduce the rate of clinical urinary infection following percutaneous nephrolithotomy.	Strong
Use antibiotic prophylaxis to reduce infectious complications in men undergoing transurethral resection of the prostate.	Strong
Use antibiotic prophylaxis to reduce infectious complications in high-risk patients undergoing transurethral resection of the bladder.	Weak
Perform prostate biopsy using the transperineal approach due to the lower risk of infectious complications.	Strong
Use routine surgical disinfection of the perineal skin for transperineal biopsy.	Strong
Use rectal cleansing with povidone-iodine in men prior to transrectal prostate biopsy.	Strong
Do not use fluoroquinolones for prostate biopsy in line with the European Commission final decision on EMEA/H/A-31/1452.	Strong
Use either target prophylaxis based on rectal swab or stool culture; augmented prophylaxis (two or more different classes of antibiotics); or alternative antibiotics (e.g. fosfomycin trometamol*, cephalosporin, aminoglycoside) for antibiotic prophylaxis for transrectal biopsy.	Weak

**Of note the indication of fosfomycin trometamol for prostate biopsy has been withdrawn in Germany as the manufacturers did not submit the necessary pharmacokinetic data in support of this indication. Urologists are advised to check their local guidance in relation to the use of fosfomycin trometamol for prostate biopsy.*

Table 13: Suggested regimens for antimicrobial prophylaxis prior to urological procedures

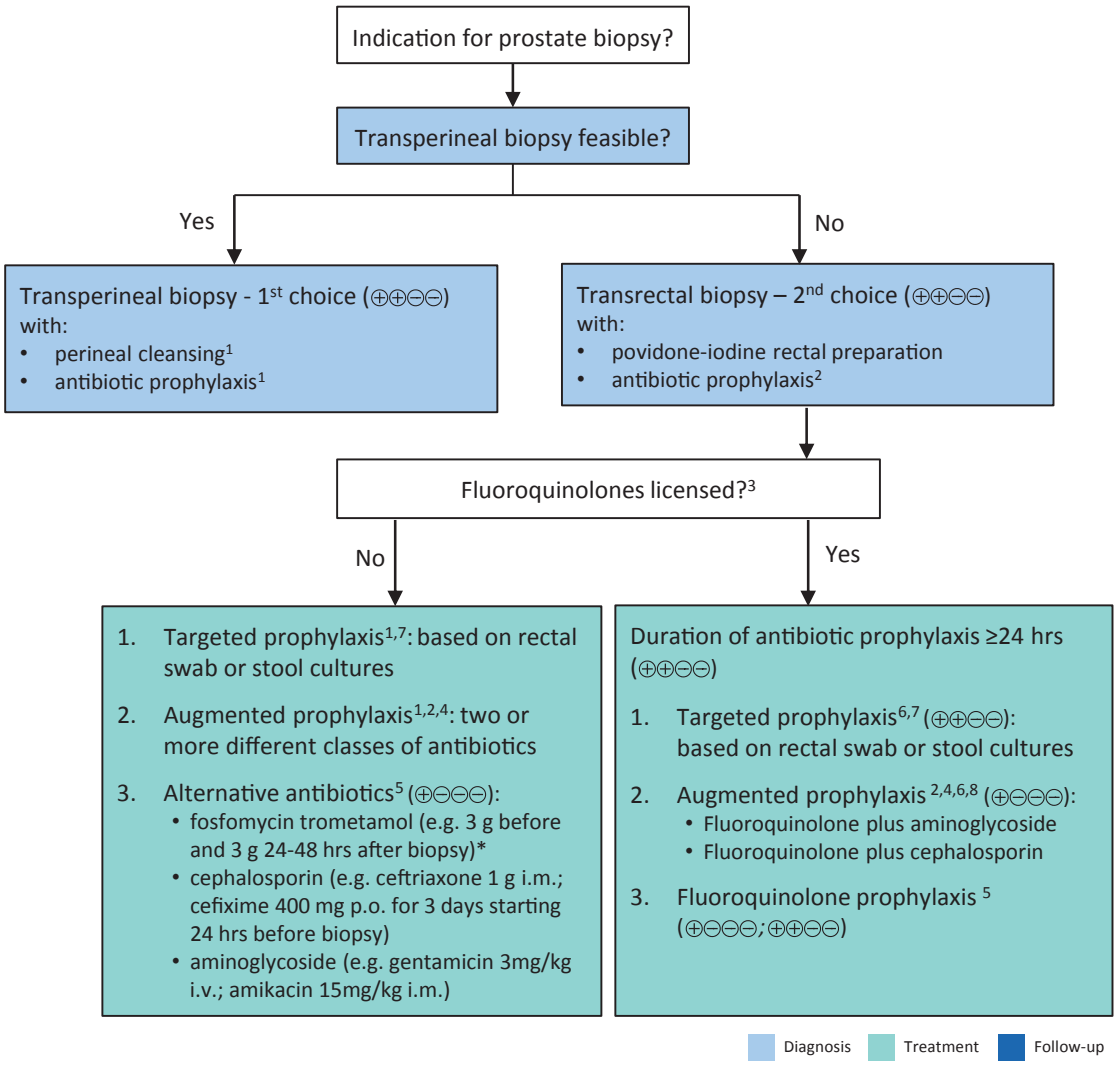
As stated in section 3.14.1.4 the panel has decided not to make recommendations for specific agents for particular procedures, those listed below represent possible choices only. Urologists should choose a specific antimicrobial based on their knowledge of local pathogen prevalence for each type of procedure, their antibiotic susceptibility profiles and virulence.

Procedure	Prophylaxis recommended	Antimicrobial
Urodynamics	No	N/A
Cystoscopy	No	
Extracorporeal shockwave lithotripsy	No	
Ureteroscopy	Yes	Trimethoprim Trimethoprim-sulphamethoxazole Cephalosporin group 2 or 3 Aminopenicillin plus a beta-lactamase inhibitor
Percutaneous nephrolithotomy	Yes (single dose)	
Transurethral resection of the prostate	Yes	
Transurethral resection of the bladder	Yes, in patients who have a high risk of suffering post-operative sepsis.	
Transrectal prostate biopsy	Yes	1. Targeted prophylaxis - based on rectal swab or stool culture. 2. Augmented prophylaxis - two or more different classes of antibiotics*. 2. Alternative antibiotics • fosfomycin trometamol** (e.g. 3 g before and 3 g 24-48 hrs after biopsy) • cephalosporin (e.g. ceftriaxone 1 g i.m.; cefixime 400 mg p.o. for 3 days starting 24 hrs before biopsy) • aminoglycoside (e.g. gentamicin 3mg/kg i.v.; amikacin 15mg/kg i.m.)

** Note option 2 is against antibiotic stewardship programmes*

*** Of note the indication of fosfomycin trometamol for prostate biopsy has been withdrawn in Germany as the manufacturers did not submit the necessary pharmacokinetic data in support of this indication. Urologists are advised to check their local guidance in relation to the use of fosfomycin trometamol for prostate biopsy.*

Figure 4: Prostate biopsy workflow to reduce infectious complications



1. *Two systematic reviews including non-RCTs and two RCTs describe comparable rates of post-biopsy infection in patients with and without antibiotic prophylaxis.*
2. *Be informed about local antimicrobial resistance.*
3. *Banned by European Commission due to side effects.*
4. *Contradicts principles of Antimicrobial Stewardship.*
5. *Fosfomycin trometamol (4 RCTs), cephalosporins (2 RCTs), aminoglycosides (2 RCTs).*
6. *Only one RCT comparing targeted and augmented prophylaxis.*
7. *Originally introduced to use alternative antibiotics in case of fluoroquinolone resistance.*
8. *Various schemes: fluoroquinolone plus aminoglycoside (4 RCTs); and fluoroquinolone plus cephalosporin (1 RCT).*
9. *Significantly inferior to targeted and augmented prophylaxis.*

GRADE Working Group grades of evidence. High certainty: (⊕⊕⊕⊕)very confident that the true effect lies close to that of the estimate of the effect. Moderate certainty: (⊕⊕⊕○)moderately confident in the effect estimate: the true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different. Low certainty: (⊕⊕○○) confidence in the effect estimate is limited: the true effect may be substantially different from the estimate of the effect. Very low certainty: (⊕○○○) very little confidence in the effect estimate: the true effect is likely to be substantially different from the estimate of effect. Figure reproduced from Pilatz et al., [573] with permission from Elsevier.

** Of note the indication of fosfomycin trometamol for prostate biopsy has been withdrawn in Germany as the manufacturers did not submit the necessary pharmacokinetic data in support of this indication. Urologists are advised to check their local guidance in relation to the use of fosfomycin trometamol for prostate biopsy*

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5. CONFLICT OF INTEREST

All members of the EAU Urological Infections Guidelines Panel have provided disclosure statements on all relationships that they have that might be perceived to be a potential source of a conflict of interest. This information is publicly 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, travel and meeting expenses. No honoraria or other reimbursements have been provided.

6. CITATION INFORMATION

The format in which to cite the EAU Guidelines will vary depending on the style guide of the journal in which the citation appears. Accordingly, the number of authors or whether, for instance, to include the publisher, location, or an ISBN number may vary.

The compilation of the complete Guidelines should be referenced as:
EAU Guidelines. Edn. presented at the EAU Annual Congress Paris 2024. ISBN 978-94-92671-23-3.

If a publisher and/or location is required, include:
EAU Guidelines Office, Arnhem, The Netherlands. http://uroweb.org/guidelines/compilations-of-all-guidelines/

References to individual guidelines should be structured in the following way:
Contributors' names. Title of resource. Publication type. ISBN. Publisher and publisher location, year.

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 Panel for Urological Trauma have prepared these guidelines in order to assist medical professionals in the management of urological trauma in adults. Paediatric trauma is addressed in the EAU Paediatric Urology Guidelines [1].

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

1.2 Panel composition

The EAU Urological Trauma Guidelines Panel consists of an international group of urologists and an interventional radiologist, all with particular expertise in urological trauma. All experts involved in the production of this document have submitted potential conflict of interest statements, which can be viewed on the EAU Website Uroweb: http://uroweb.org/guideline/urological-trauma/?type=panel.

1.3 Available publications

A quick reference document, the Pocket Guidelines, is available in print and on the EAU Website. This is an abridged version which may require consultation together with the full text version. A number of translated versions, alongside several scientific publications in European Urology, the Associations scientific journal, are also available [2-5]. All documents can be viewed through the EAU website: http://uroweb.org/guideline/urological-trauma/.

1.4 Publication history

The Urological Trauma Guidelines were first published in 2003. All sections of the 2023 Urological Trauma Guidelines have been fully updated. The next update of the Urological Trauma Guidelines will be published in 2025.

2. METHODS

2.1 Evidence sources

For the 2023 Urological Trauma Guidelines, new and relevant evidence has been identified, collated and appraised through a structured assessment of the literature. A broad and comprehensive literature search, covering all sections of the Urological Trauma Guidelines was performed. Databases searched included Medline, EMBASE, and the Cochrane Libraries, covering a time frame between May 1st, 2021, and April 29th, 2022. A total of 1,236 unique records were identified, retrieved and screened for relevance. A detailed search strategy is available online: http://uroweb.org/guideline/urological-trauma/?type=appendices-publications. The majority of identified publications were comprised of case reports and retrospective case series. The lack of high-powered randomised controlled trials (RCTs) makes it difficult to draw meaningful conclusions. The panel recognises this critical limitation.

Recommendation within the Guidelines are developed by the panels to prioritise clinically important care decisions. The strength of each recommendation is determined by the balance between desirable and undesirable consequences of alternative management strategies, the quality of the evidence (including certainty of estimates), and the nature and variability of patient values and preferences [6, 7]. This decision process, which can be reviewed in the strength rating forms which accompany each guideline statement, addresses a number of key elements:

1. the overall quality of the evidence which exists for the recommendation [8];
2. the magnitude of the effect (individual or combined effects);
3. the certainty of the results (precision, consistency, heterogeneity and other statistical or study related factors);
4. the balance between desirable and undesirable outcomes;
5. the impact of patient values and preferences on the intervention.

Strong recommendations typically indicate a high degree of evidence quality and/or a favourable balance of benefit to harm and patient preference. Weak recommendations typically indicate availability of lower quality evidence, and/or equivocal balance between benefit and harm, and uncertainty or variability of patient preference [9].

Additional information can be found in the general Methodology section of this print, and online at the EAU website; http://www.uroweb.org/guideline/. A list of associations endorsing the EAU Guidelines can also be viewed online at the above address.

2.2 Peer review

The Urological trauma Guidelines was peer reviewed prior to publication in 2019.

3. EPIDEMIOLOGY, CLASSIFICATION & GENERAL MANAGEMNET PRINCIPALS

3.1 Definition and Epidemiology

Trauma is defined as a physical injury or a wound to living tissue caused by an extrinsic agent. Worldwide, there are over four million injury-related deaths ever year which constitute nearly 8% of all deaths [10]. About 25% of them are violence related. For young people (5 - 29 years old), three of the top five causes of death are injury-related (road traffic injuries, homicide, and suicide). Tens of millions more people suffer non-fatal injuries each year which lead to acute care visits, hospitalizations, and often result in temporary or permanent disability and the need for long-term physical and mental health care and rehabilitation. Twice as many males than females are killed each year because of injuries and violence [10].

Trauma is therefore a serious public health problem with significant social and economic costs. Considerable variation exists in the causes and the effects of traumatic injuries between geographical areas, as well as between low, middle, and high-income countries with about 90% of injury-related deaths occur in low- and middle-income countries [10].

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 road traffic accidents/injury, falls, and other domestic accidents). Intentional trauma accounts for approximately half of the trauma-related deaths worldwide [11]. A specific type of unintentional injury is iatrogenic injury which occurs 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 due to a temporary expansive cavitation that causes destruction in a much larger area than the projectile tract itself. In lower velocity injuries, the damage is usually confined to the projectile tract. Blast injury is a complex cause of trauma which includes blunt and penetrating trauma and burns.

The most commonly used classification grading system is the AAST (American Association for the Surgery of Trauma) injury scoring scale [12]. It is useful for managing renal trauma, but for the other urological organs, the injuries are commonly described by their anatomical site and severity (partial/complete).

3.3 General management principals

*3.3.1 **The Initial evaluation***

The initial emergency assessment of a trauma patient is beyond the focus of these guidelines. It is usually carried out by emergency medicine and trauma specialised personnel following advanced trauma life support (ATLS) principles. Detailed further assessment involves cross-sectional imaging, laboratory analysis and specialist surgical input. The management of individual organ injury will follow in the sections below. Tetanus vaccine status should be assessed for all penetrating injuries.

3.3.2 ***Polytrauma managed in major trauma centres leads to improved survival***

Urological trauma is often associated with significant injuries in the polytraumatised patient [13]. Lessons from civilian trauma networks, military conflict, and mass casualty events have led to many advances in trauma care [14-16]. These include the widespread acceptance of damage control principles and trauma centralisation to major trauma centres staffed by dedicated trauma teams. The re-organisation of care to these centres has been shown to reduce mortality by 25% and length of stay by four days [14]. Urologists increasingly understand their role in the context of polytrauma with the ultimate aims of improving survivability and decreasing morbidity in these patients.

3.3.3 ***Damage control***

Damage control is a life-saving strategy for severely injured patients that recognises the consequences of the lethal triad of trauma - hypothermia, coagulopathy, and acidosis [17-19]. The first of a three phased approach 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 final stage involves definitive surgery when more time-consuming reconstructive procedures are performed in the stabilised patient [20]. Urological intervention needs to be mindful of the phase of management. Temporary abbreviated measures followed by later definitive surgery are required. Complex reconstructive procedures, including organ preservation, are not undertaken. The decision to enter damage control mode is taken by the lead trauma clinician following team discussion.

Urological examples include haemodynamically unstable patients due to suspected renal haemorrhage or pelvic fracture with associated urethral or bladder injury. The options of abdominal packing and temporary urinary drainage by ureteric, bladder or urethral catheterisation are valuable adjuncts to care.

3.3.4 ***Mass casualty events and Triage***

A mass casualty event is one in which the number of injured people and the severity of their injuries exceed the capacity of the facility and staff [21]. Triage, communication, and preparedness are important components for a successful response.

Triage after mass casualty events 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 and from those whose injuries are so severe that survival is unlikely in the circumstances [22, 23].

3.3.5 ***The role of thromboprophylaxis and bed rest***

Trauma patients are at high risk of deep venous thrombosis (DVT). Concerns about secondary haemorrhage result in prolonged post-injury bed rest DVT which effectively compounds this risk. Established prophylaxis measures reduce thrombosis and are recommended following systemic review [24]. However, the strength of evidence is not high and as yet there is no evidence to suggest that mortality or pulmonary embolism risk is reduced [25]. Compression stockings and low molecular weight heparins are favoured. The risk of secondary haemorrhage in isolated renal trauma is low and the practice of strict bed rest has waned in patients who are able to mobilise [26].

3.3.6 ***Antibiotic stewardship***

Single shot antibiotic doses are common in major trauma. The indication for continuing antibiotics is governed by injury grade, associated injuries and the need for intervention. Patients with urinary extravasation tend to be kept on antibiotics but there is no evidence base for this. Antibiotics should be avoided in lesser trauma e.g. Grade 1-3 renal trauma, and regular review should be undertaken for those continued on antibiotics.

3.3.7 ***Urinary catheterisation***

Prolonged catheterisation is required in all forms of bladder and urethral injury. Catheterisation is not necessary in stable patients with low-grade renal injury. Patients with heavy haematuria, who require monitoring or ureteric stenting, benefit from catheterisation. This can be removed once haematuria lightens and there is an improvement in the clinical situation. The shortest possible period of catheterisation is advised.

4. UROGENITAL TRAUMA GUIDELINES

4.1 Renal Trauma

4.1.1 Epidemiology, aetiology and pathophysiology

Renal trauma is present in up to 5% of all trauma cases [27]. It is most common in young males and has an overall population incidence of 4.9 per 100,000 [28]. Most injuries can be managed non-operatively with successful organ preservation [29, 30].

Blunt injuries result from road traffic accidents/injury, falls, sporting injuries, and assault [31]. The kidney and/or hilar structures are directly crushed as a result. Less commonly, sudden deceleration may result in an avulsion injury affecting the vascular structures of the hilum or the ureteropelvic junction (UPJ).

Penetrating injuries are due to stab and gunshot wounds. They tend to be more severe and less predictable than blunt trauma. The prevalence is higher in urban settings [32]. Penetrating injury produces direct tissue disruption of the parenchyma, vascular pedicles, or collecting system. High-velocity bullets or fragments have the potential for greatest parenchymal destruction and are most often associated with multiple-organ injuries [33].

The most commonly used classification system is that of the AAST [12]. It is validated and predicts morbidity and the need for intervention [34, 35]. This remains the most useful of urological trauma classifications; however, the majority of Grade 1-4 injuries are now managed conservatively and debate has centred around updating the classification of high-grade injury i.e. identifying the injuries most likely to benefit from early angiographic embolisation, repair or nephrectomy [29, 36].

Table 4.1.1: Extract of the AAST renal injury grading scale [37]

Grade*	Type of injury	Description of injury
1	Haematoma and/or Contusion	Subcapsular non-expanding haematoma or parenchymal contusion without parenchymal laceration.
2	Haematoma	Non-expanding perirenal haematoma confined to Gerota fascia.
	Laceration	Renal parenchymal laceration ≤ 1 cm depth without urinary extravasation.
3	Laceration	Renal parenchymal laceration ≤ 1 cm depth without collecting system rupture or urinary extravasation. Any injury in the presence of a kidney vascular injury or active bleeding contained within Gerota fascia.
4	Laceration	Parenchymal laceration extending into urinary collecting system with urinary extravasation. Renal pelvis laceration and/or complete ureteropelvic disruption.
	Vascular	Segmental renal vein or artery injury. Active bleeding beyond Gerota fascia into the retroperitoneum or peritoneum. Segmental or complete kidney infarction(s) due to vessel thrombosis without active bleeding.
5	Laceration	Shattered kidney with loss of identifiable parenchymal renal anatomy.
	Vascular	Main renal artery or vein laceration or avulsion of renal hilum. Devascularised kidney with active bleeding.

**Advance one grade for bilateral injuries up to Grade 3.*

Note: The AAST renal injury scale was updated in 2018 and is presented in Table 4.1.1; however, all references included in this text are based on the AAST 1989 renal injury scale. The 2018 injury scale does not outperform the previous grading system in predicting bleeding and the need for treatment intervention and does not impact on the validity of the current recommendations [38].

4.1.2 Evaluation

The evaluation of stable patients with suspected renal trauma is now based on a trauma protocol computed tomography (CT) scan, often performed prior to involvement of a urologist [39, 40]. It is important to consider all parameters in the evaluation of the patient and to understand the indications for scanning when these are not absolute. Indicators of injury include a direct blow to the flank or rapid deceleration event (fall, high-speed road traffic accidents). Special consideration should be given to pre-existing renal disease [41] or the injured solitary kidney [42]. Pre-existing abnormality e.g. hydronephrosis makes injury more likely following trauma [43].

Vital signs should be recorded throughout the initial evaluation and give the most reliable indication of the urgency of the situation. Physical examination may reveal flank bruising, stab wounds, or bullet entry or exit wounds and abdominal tenderness.

Urinalysis, haematocrit and baseline creatinine are required. Haematuria (visible or non-visible) is the key finding. However, major injury such as disruption of the UPJ, pedicle injuries, segmental arterial thrombosis and stab wounds may not have haematuria [44, 45]. Haematuria that is out of proportion to the history of trauma may suggest pre-existing pathology [46]. Urine dipstick quickly evaluates for haematuria, but false-negative results can range from 3-10% [47]. An increased creatinine level usually reflects pre-existing renal pathology.

*4.1.3 **Imaging: criteria for radiographic assessment***

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 intervention. The majority of patients with moderate to major trauma will have had a CT scan performed soon after presentation. In patients who have not had any imaging the indications for renal imaging are [31, 48-51]:

- visible haematuria;
- non-visible haematuria and one episode of hypotension;
- a history of rapid deceleration injury and/or significant associated injuries;
- penetrating trauma;
- clinical signs suggesting renal trauma e.g. flank pain, abrasions, fractured ribs, abdominal distension and/or a mass and tenderness.

4.1.3.1 Computed tomography

Computed tomography is the imaging modality of choice in stable patients. It is quick, widely available, and can accurately identify grade of renal injury [52], establish the presence of the contralateral kidney and demonstrate concurrent injuries to other organs. It is ideally performed as a three-phase study [53]:

1. The arterial phase assesses vascular injury and presence of active extravasation of contrast.
2. The nephrographic phase optimally demonstrates parenchymal contusions and lacerations.
3. The delayed phase imaging (five minutes) identifies collecting system/ureteric injury.

In practice, trauma patients usually undergo standardised whole-body imaging protocols and delayed phase imaging of the renal tract is not routinely performed. If there is suspicion that renal injuries have not been fully evaluated, delayed phase imaging is recommended. The rates of contrast-induced nephropathy seen in trauma patients is low [54].

4.1.3.2 Ultrasonography (US)

In the primary survey of a critically injured patient, FAST (Focused Assessment Sonography in Trauma) is used to identify hemoperitoneum as the cause of haemorrhage and hypovolemia. However, it is not routinely used for the assessment of solid organ injury as it is insensitive, operator dependant, does not define the injury well, and is inferior to CT. It is an option for follow-up [55-57].

4.1.3.3 Other imaging modalities

4.1.3.3.1 Intravenous pyelography (IVP)

Intravenous pyelography and radionuclide scans and magnetic resonance imaging (MRI) do not have a significant role in the trauma setting. The quality of one shot IVP is generally poor. Palpation of the contralateral (unaffected) kidney is a pragmatic surrogate of function [18].

The diagnostic accuracy of MRI in renal trauma is similar to that of CT [58, 59]. However, the logistical challenges of MRI make this modality impractical in acute trauma.

*4.1.4 **Disease management***

4.1.4.1 Non-operative management

The non-operative management of renal trauma can be viewed as a “package of care”; a stepwise approach starting with conservative treatment, followed by minimally invasive and/or surgical exploration, if necessary. It should be noted that an algorithm for “package of care” will vary in different centres according to available interventions; however, the importance of escalation in treatment interventions should be emphasised [29]. This approach has likely resulted in the rate of nephrectomy for high-grade renal injuries decreasing over time [60].

4.1.4.1.1 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 cases. In stable patients, this means a period of bed rest, serial blood tests, regular observation and re-imaging as indicated [26]. Primary conservative management is associated with a lower rate of nephrectomies, and no increase in immediate or long-term morbidity [61].

Grade 1-3 injuries are managed non-operatively [62, 63]. Grade 4 injuries are also mostly treated conservatively, but the requirement for subsequent intervention is higher [64]. Persistent urinary extravasation from an otherwise viable kidney after blunt trauma usually responds to stent placement and/or percutaneous drainage [65].

Grade 5 injuries often present with haemodynamic instability and major associated injuries. There is thus a higher rate of exploration and nephrectomy [66, 67]. However, several studies now support expectant management in patients with Grade 4 and 5 injuries [29, 30, 68-72]. Similarly, unilateral main arterial injuries or arterial thrombosis are normally managed non-operatively in haemodynamically stable patients with surgical repair reserved for bilateral artery injuries or injuries involving a solitary functional kidney [73]. Pre-hospital prolonged warm ischaemia usually results in irreparable damage and renal loss.

One study designed a nomogram to predict the need for an intervention to stop bleeding in high-grade renal trauma. Factors which increased risk of intervention were a haematoma size of > 12 cm, penetrating trauma, vascular contrast extravasation, pararenal haematoma extension, concomitant injuries, and shock [74].

4.1.4.1.2 Penetrating renal injuries

Penetrating abdominal wounds have traditionally been managed surgically. However, selective non-operative management of penetrating abdominal wounds is now accepted following detailed assessment in stable patients [64, 75-77].

For renal injuries, the site of the wound, haemodynamic stability, and diagnostic imaging are the main determinants for intervention. The majority of low-grade stab wounds posterior to the anterior axillary line can be managed non-operatively in stable patients [78]. Grade 3 or higher injuries due to stab wounds in stable patients can be managed expectantly but warrant closer observation as the clinical course is more unpredictable and associated with a higher rate of delayed intervention [78, 79]. High-grade injuries, concomitant abdominal injuries and gunshot wounds are most likely to fail non-operative management [77]. A gunshot wound is an independent risk factor for nephrectomy in grade IV and V traumatic renal injuries, compared with stab wounds [80]. Overall, non-operative management of penetrating injuries in selected stable patients is associated with a successful outcome in up to 50% of stab wounds and up to 40% of gunshot wounds [30, 81-84].

4.1.4.1.3 Selective angioembolisation

Selective angioembolisation (AE) has a key role in the non-operative management of blunt renal trauma in haemodynamically stable patients [85]. Currently there are no validated criteria to identify patients who require AE and its use in renal trauma remains variable. Accepted CT findings indicating the need for AE are active extravasation of contrast, arteriovenous fistula (AVF) and pseudo-aneurysm [86]. The presence of both active extravasation of contrast and a large haematoma (> 25 mm depth) predict the need for AE with good accuracy [86, 87].

Angioembolisation has been utilised in the non-operative management of all grades of renal injury; however, it is likely to be most beneficial in the setting of high-grade renal trauma (AAST > 3) [88-90]. Non-operative management of high-grade renal trauma, where AE is included in the management algorithm, can be successful in up to 94.9% of Grade 3, 89% of Grade 4 and 76% of Grade 5 injuries [85, 88, 91-93]. Increasing grade of renal injury is associated with increased risk of failed AE and need for repeat intervention [94]. Gross haematuria, haemodynamic instability, Grade 5 trauma and urinary extravasation are significant predictors of AE failure [95].

Repeat embolisation prevents nephrectomy in 67% of patients. Open surgery after failed embolisation usually results in nephrectomy [94, 96]. Despite concerns regarding parenchymal infarction and the use of iodinated contrast media, AE does not appear to affect the occurrence or outcome of acute kidney injury following renal trauma [97]. For high-grade injuries, AE has also been shown to have a high success rate and to provide the greatest protection of renal function, with no difference in renal function after long-term follow-up [98]. In severe polytrauma or high operative risk, the main artery may be embolised, either as a definitive treatment or as a step to a more controlled nephrectomy.

The evidence supporting AE in penetrating renal trauma is sparse. One study found that AE is three times more likely to fail in penetrating trauma [75]. However, AE has been used successfully to treat acute haemorrhage, AVF and pseudo-aneurysms resulting from penetrating renal trauma [99].

4.1.4.1.4 Ureteral stenting and urinary catheterisation

In the management of high-grade renal trauma with collecting system injuries, ureteral stenting in asymptomatic patients has proven no clear benefits. Current evidence suggests intervention (ureteral stenting, nephrostomy or perirenal drainage) only when patients develop symptoms (flank pain, fever, leucocytosis) related with persistent urinary leaks [65, 100].

Catheterisation is not necessary in stable patients with low-grade injury. Patients with severe visible haematuria, who require monitoring or stenting, benefit from catheterisation. A longer period of catheterisation is required if a stent is placed. Once the haematuria lightens and the patient is mobile, the catheter should be removed.

4.1.4.1.5 Repeat imaging (early)

Computed tomography scans should be performed on patients with fever, unexplained decreased haematocrit, or significant flank pain. Repeat imaging is also recommended in high-grade injury and in penetrating trauma two to four days after trauma to minimise the risk of missed complications. Repeat imaging can be safely omitted for patients with Grade 1-3 injuries as long as they remain clinically well [101, 102].

4.1.4.2 Surgical management

4.1.4.2.1 Indications for renal exploration

A non- or transient- response to initial fluid resuscitation is a strong indication for exploration [75, 76]. There is a trend towards ongoing resuscitation and AE [103]. Exploration is influenced by aetiology and grade of injury, transfusion requirements, the need to explore associated abdominal injuries, and the discovery of an expanding or pulsatile peri-renal haematoma at laparotomy [104]. Haemodynamic instable grade 5 vascular injuries are an indication for exploration [91, 105].

4.1.4.2.2 Operative findings and reconstruction

The overall exploration rate for blunt trauma is low [106]. The goals of exploration following renal trauma are vascular control and renal salvage. Most series recommend the transperitoneal approach for surgery [107, 108]. Entering the retroperitoneum and leaving the confined haematoma undisturbed within the perinephric fascia is recommended; temporarily packing the fossa tightly with laparotomy pads can salvage the kidney in instances of intra-operative haemorrhage [109]. 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 [109].

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 and warrant further exploration [110].

Feasibility of renal reconstruction should be judged during the operation. The overall rate of patients who undergo a nephrectomy during exploration is approximately 30% [111]. Other intra-abdominal injuries also increase the likelihood of nephrectomy [112]. Mortality is associated with overall severity of the injury and not often a consequence of the renal injury itself [113]. High velocity gunshot injuries make reconstruction difficult and nephrectomy is usually required [114].

Renorrhaphy is the most common reconstructive technique. Partial nephrectomy is required when non-viable tissue is detected. Watertight closure of the collecting system is desirable, although closing the parenchyma over the injured collecting system is acceptable.

The use of haemostatic agents and sealants in reconstruction is helpful [115]. In all cases, drainage of the ipsilateral retroperitoneum is recommended.

The repair of vascular injuries is seldom, if ever, effective [116]. Repair should be attempted in patients with a solitary kidney or bilateral injuries [117]. 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. Bleeding or dissection of the main renal artery may also be managed with a stent.

4.1.5 ***Follow-up***

The risk of complications relates to aetiology, injury grade, and mode of management [118, 119]. Follow-up includes physical examination, urinalysis, diagnostic imaging, blood pressure measurement and serum creatinine [66]. Potential complications are primarily identified by imaging; however, follow-up imaging is not recommended in low-grade uncomplicated injury. Ultrasound can be used to define the post-injury anatomy avoiding further ionising radiation. Nuclear scans are useful for documenting functional recovery following renal injury and reconstruction [120]. Annual blood pressure monitoring is recommended to exclude renovascular hypertension [121].

4.1.5.1 Complications

Early (≤ 1 month) complications include bleeding, infection, perinephric abscess, sepsis, urinary fistula, hypertension, urinary extravasation, and urinoma. Delayed complications include bleeding, calculus formation, chronic pyelonephritis, hypertension, AVF, hydronephrosis and pseudo-aneurysms. Bleeding may be life-threatening with elective angiographic embolisation the preferred treatment [122]. Perinephric abscess formation is initially managed by percutaneous drainage [106].

Hypertension is rare [123, 124]. It may occur acutely because of external compression from peri-renal haematoma (Page kidney), chronically due to compressive scar formation, or as a result of renal artery thrombosis, segmental arterial thrombosis, renal artery stenosis (Goldblatt kidney), or AVF. Arteriography may be required. Treatment, including medical management, excision of the ischaemic parenchymal segment, vascular reconstruction, or nephrectomy, is indicated if hypertension persists [121].

Arteriovenous fistulae usually present with delayed onset of significant haematuria, most often after penetrating trauma. Percutaneous embolisation is often effective for symptomatic AVF, but larger fistulae may require surgery [125]. The development of pseudo-aneurysm is a rare complication following blunt trauma.

*4.1.6 **Iatrogenic renal injuries***

Iatrogenic renal trauma needs to be recognised and managed promptly to minimise morbidity and mortality. The most common causes of iatrogenic renal injuries are percutaneous access to kidney, stone surgery, cancer surgery (laparoscopic and open) and transplantation [3]. The diagnosis and management follow the same principles as outlined previously.

*4.1.7 **Summary of evidence and recommendations for evaluation and management of renal trauma***

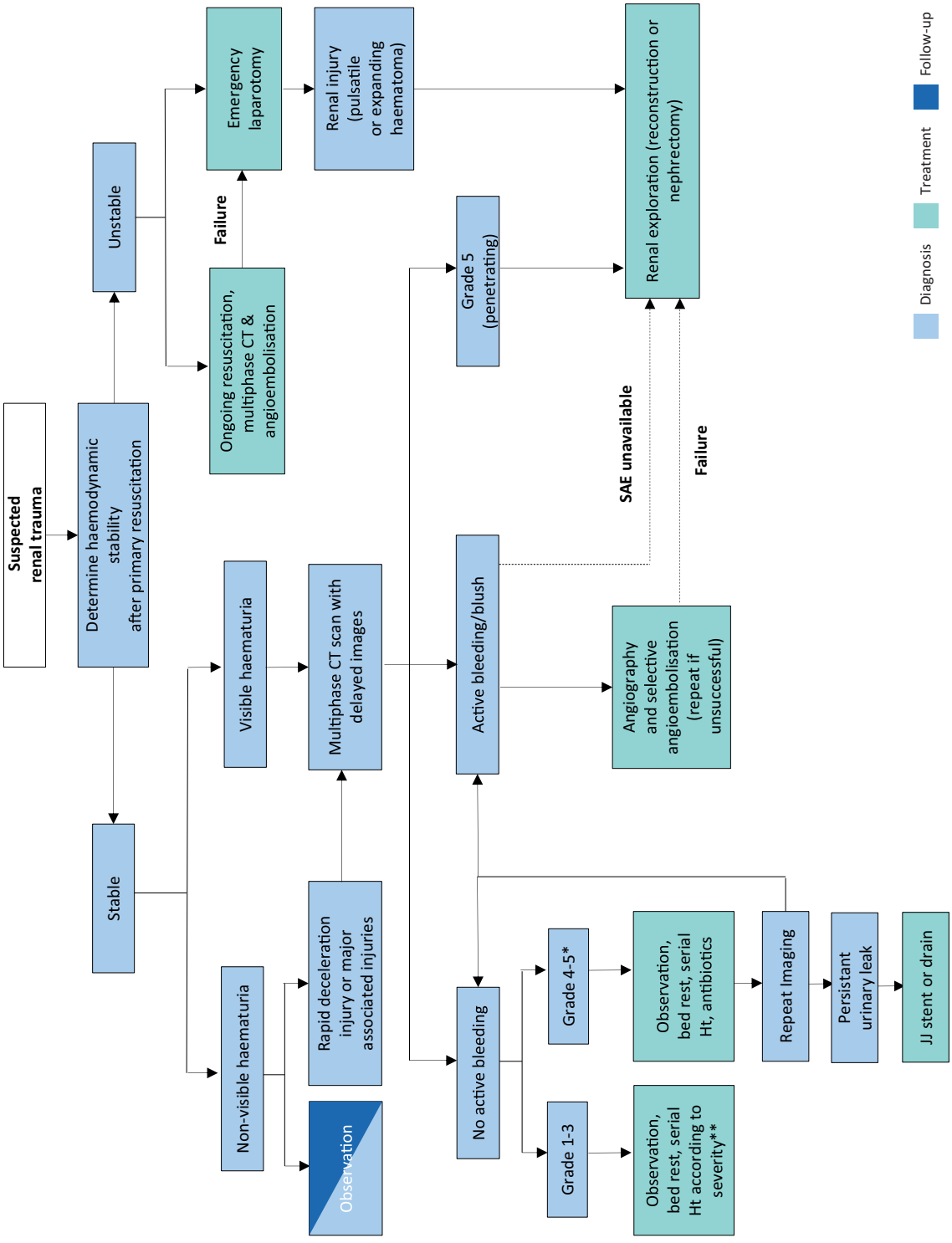
Summary of evidence	**LE**
Vital signs on admission give the most reliable indication of the urgency of the situation.	3
Special consideration should be given to patients with a solitary kidney and pre-existing renal disease.	4
Haematuria is a key finding following renal trauma; although, it may not be present in certain situations.	3
A multiphase CT scan is the best method for the diagnosis and staging of renal injuries in haemodynamically stable patients.	3
Haemodynamic stability is the primary criterion for selecting patients for non-operative management.	3
Ureteric stenting in stable asymptomatic Grade 4 renal injuries is not necessary.	3
Selective angioembolisation is effective in patients with active bleeding from renal injury, without other indications for immediate abdominal operation.	3
Renal reconstruction should be attempted if haemorrhage is controlled and there is sufficient viable renal parenchyma.	3
Iatrogenic renal injuries are procedure-dependent (1.8-15%); the most common injuries are vascular.	3
Limited literature exists with regard to long-term consequences of renal trauma. Current follow-up includes physical examination, urinalysis, diagnostic imaging, serum creatinine, as well as annual blood pressure monitoring to diagnose renovascular hypertension.	4

Recommendations	Strength rating
Evaluation	
Assess haemodynamic stability upon admission.	Strong
Record past renal surgery, and known pre-existing renal abnormalities (ureteropelvic junction obstruction, solitary kidney, urolithiasis).	Strong
Test for haematuria in a patient with suspected renal injury.	Strong
Perform a multiphase computed tomography (CT) scan in trauma patients with: • visible haematuria; • non-visible haematuria and one episode of hypotension; • a history of rapid deceleration injury and/or significant associated injuries; • penetrating trauma; • clinical signs suggesting renal trauma e.g. flank pain, abrasions, fractured ribs, abdominal distension and/or a mass and tenderness.	Strong
Management	
Manage stable patients with blunt renal trauma non-operatively with close monitoring and re-imaging as required.	Strong
Manage isolated Grade 1-4 stab and low-velocity gunshot wounds in stable patients non-operatively.	Strong
Use selective angioembolisation for active renal bleeding if there are no other indications for immediate surgical exploration.	Strong
Insert urinary system drainage (ureteral stenting, nephrostomy) or perirenal drainage in cases of persistent or symptomatic urinary leak.	Strong
Proceed with renal exploration in the presence of: • persistent haemodynamic instability; • Grade 5 vascular or penetrating injury; • expanding or pulsatile peri-renal haematoma.	Strong
Attempt renal reconstruction if haemorrhage is controlled and there is sufficient viable renal parenchyma.	Weak
Repeat imaging in high-grade and penetrating injuries and in cases of fever, worsening flank pain, or falling haematocrit.	Strong
Follow-up approximately three months after major renal injury with urinalysis, individualised radiological investigation eg.: nuclear scintigraphy, CT or ultrasound, blood pressure measurement and renal function tests. Longer term annual follow-up for blood pressure is recommended.	Weak

*4.1.8 **Treatment algorithms***

Management of renal trauma

Figure 4.1.1 Management of renal trauma



** Excluding Grade 5 penetrating injuries.*

*** Antibiotics should be administered for all penetrating injuries.*

--- If haemodynamically unstable.

CT = computed tomography; Ht = haematocrit; SAE = selective angioembolisation.

4.2 Ureteral Trauma

*4.2.1 **Incidence***

Trauma to the ureters is relatively rare as they are protected by their small size, mobility, posterior location, and the adjacent musculoskeletal and visceral structures. Iatrogenic injury during open, laparoscopic and endoscopic surgery is responsible for the majority of cases [126]. The injury is often missed intra-operatively and may result in significant morbidity [127].

*4.2.2 **Epidemiology, aetiology, and pathophysiology***

Overall, ureteral trauma accounts for 1-2.5% of urinary tract trauma [126, 128-130], Penetrating external ureteral trauma, mostly by gunshot wounds, is the commonest form in most modern series, [126, 128, 131]. Higher rates of ureteral injury are seen in modern combat injuries [127]. About one-third of cases of external trauma to the ureters are caused by blunt trauma, mostly road traffic accidents [129, 130].

Ureteral injury should be suspected in all cases of penetrating abdominal injury, although it occurs in just 2-3% of cases [126]. It should also be suspected in blunt trauma with significant deceleration as pelvi-ureteral disruption can result. [126]. The distribution of external ureteral injuries along the ureter varies between series, but it is commonest in the upper ureter [128-130].

The incidence of urological iatrogenic trauma has decreased in the last twenty years due to improvements in technique, instrument technology, training methods and subspecialisation [131, 132].

Iatrogenic ureteral trauma can result from:
- ligation with a suture,
- rushing by a surgical instrument,
- partial or complete transection by unintended scalpel incision,
- thermal injury,
- or ischaemia from devascularisation [131, 133, 134].

Injury usually involves the lower ureter [126, 131, 133, 135]. Gynaecological operations are the most common cause of significant iatrogenic trauma (Table 4.2.1). It also occurs in colorectal operations, (resection of the distal colon) and vascular surgery (aortic aneurysm repair) [136, 137]. There has been a significant decrease in the rate of ureteral injury during robot-assisted procedures [138] and colorectal surgery [42]. However, minimally invasive techniques have not further reduced the rate of ureteral injuries in gynaecological surgery [139-141].

Ureteroscopy is a common cause of iatrogenic ureteric trauma contributing up to 71.6% in some series [142]. The post-ureteroscopic lesion scale (PULS) aims to standardise intra-operative traumatic findings during ureteroscopy [143]. Predictors for high grade ureteric injury include male gender, longer operative times, and ureteral access sheath (UAS) insertion times [142].

A smaller proximal ureter diameter seen in CT scanning and a predictor for high-grade ureteral injury during ureteral access sheath (UAS) placement [144]. A small RCT using pre-operative silodosin 8 mg for three days significantly reduced Grade 2 or higher ureteral injuries due to UAS insertion [145].

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 [131, 136, 146, 147]. Occult ureteral injury occurs more often than reported and not all injuries are diagnosed intra-operatively [127].

Table 4.2.1: Incidence of ureteral injury in various procedures

Procedure	Percentage %
Gynaecological [135, 148-150]	
Emergency caesarean delivery	0.01-0.06
Vaginal hysterectomy	0.02-0.5
Abdominal hysterectomy	0.03-2.0
Laparoscopic hysterectomy	0.13-6.0
Urogynaecological (anti-incontinence/prolapse)	1.7-4.3
Colorectal [134, 138, 148, 151, 152]	0.15-10
Ureteroscopy [132]	

Mucosal abrasion	0.3-4.1
Ureteral perforation	0.2-2.0
Intussusception/avulsion	0-0.3
Post-chemotherapy lymph node dissection for non-seminoma germ cell tumours	0.02
Radical prostatectomy [154]	
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 best identified intra-operatively during laparotomy [155]. The diagnosis is delayed in most cases of blunt trauma and iatrogenic trauma [131, 135, 156].

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 spinal injuries [129, 130]. Haematuria is an unreliable and poor indicator of ureteral injury, as it is present in only 50-75% of patients [126, 131, 157].

Iatrogenic injury may be noticed during the primary procedure, when intravenous dye (e.g. indigo carmine) is injected to exclude ureteral injury. Early recognition facilitates immediate repair and provides a better outcome [146, 155]. However, it is usually presenting later in the same admission, with the untoward sequelae of ureteral injury - upper tract obstruction, sepsis, abdominal distension, and 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, and uraemia or urinoma. The complication rate increases with delayed diagnosis [126, 156, 158].

4.2.3.2 Radiological diagnosis

Multi-phase CT is the mainstay imaging technique for trauma patients. Generally, it is widely available and allows for multi-phasic assessment of all of the structures in the pelvis and abdomen. Computed tomography urography (CTU) is the examination of choice when ureteral injuries are suspected [159, 160]. Extravasation of contrast medium in the delayed phase is the hallmark sign of injury. However, hydronephrosis, ascites, urinoma or mild ureteral dilation are often the only signs. In unclear cases, a retrograde or antegrade urography is the best method for confirmation [131]. Intravenous pyelography, especially one-shot IVP, is unreliable in diagnosis, as it is negative in up to 60% of patients [126, 131].

*4.2.4 **Prevention of iatrogenic trauma***

The prevention of iatrogenic trauma to the ureters depends upon the visual identification of the ureters and careful intra-operative dissection in their proximity [131, 133, 134]. The use of prophylactic pre-operative ureteral stent insertion assists in visualisation and palpation can be used in cases of higher complexity [37, 161]. It is probably makes it easier to detect ureteral injury intra-operatively [133]; however, it is not associated with a decrease in the likelihood of ureteric injury [152]. Apart from its evident disadvantages (potential complications, increased surgical time and cost), a stent may alter the location of the ureter and diminish its flexibility [133, 151]. A retrograde instillation of indocyanine green in the ureters has been shown to safely allow their identification and preservation in complex robotic-assisted colorectal surgeries [162, 163].

*4.2.5 **Management***

Management of ureteral trauma depends on many factors including the aetiology, 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 urinary diversion via a nephrostomy tube. Stenting is helpful because it provides canalisation and may decrease the risk of stricture [131, 164, 165]. Immediate repair of complete ureteral injury is advisable as it significantly decreases the need for secondary or tertiary procedures compared to delayed repair [164]. The ureter is mobilised on both ends and a spatulated end-to-end anastomosis is performed. Primary repair by uretero-ureterostomy or ureteric re-implantation can be safely performed laparoscopically at the time of the iatrogenic injury, with good medium-term results [166]. In cases of unstable trauma patients, a 'damage control' approach is preferred with ligation of the ureter, diversion of the urine (e.g. via a nephrostomy), and a later delayed definitive repair [167]. A national trauma

database study reported that the majority of blunt low- and high-severity traumatic ureteric injuries in both stable and unstable patients were treated by nephrostomy or stenting [168]. Exploratory laparotomy for associated traumatic injuries was a predictor for immediate ureteral reconstruction [168]. Injuries that are diagnosed late are usually managed first by placement of a nephrostomy tube or stent [131].

Endo-urological treatment of delayed-diagnosed ureteral injuries by internal stenting, with or without dilatation, is the first step in most cases. It is performed either retrogradely or antegradely via a percutaneous nephrostomy, and it has a variable success rate of 14-19% [169-171]. An open or robot-assisted laparoscopic surgical repair is necessary in case of failure [172]. 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 [126]. When this approach is not feasible, a ureterocalicostomy should be considered. In case of a large extra-renal pelvis and a stricture at the UPJ, a pelvic spiral flap (Culp de Weerd) is an option [173]. In extensive ureteral loss, a transureteroureterostomy is a valid option. The proximal stump of the ureter is transposed across the midline and anastomosed to the contralateral ureter. The reported stenosis rate is 4% and re-intervention or revision occurs in 10% of cases [174].

4.2.5.2 Distal ureteral injury

Distal injuries are best managed by ureteral re-implantation (ureteroneocystostomy) because the primary trauma jeopardises the blood supply to the distal ureter. The question of refluxing vs. non-refluxing ureteral re-implantation remains unresolved in the literature. The risk for clinically significant reflux should be weighed against the risk for ureteral obstruction.

A psoas hitch between the bladder and the ipsilateral psoas tendon is usually needed to bridge the gap and to protect the anastomosis from tension. The contralateral superior vesical pedicle may be divided to improve bladder mobility. The reported success rate is very high (97%) [174]. In extensive mid-lower ureteral injury, the large gap can be bridged with a tabularised L-shaped bladder flap (Boari flap). It is a time-consuming operation and unsuited to the acute setting. The success rate is reported to be 81-88% [175].

4.2.5.3 Long segment 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 includes serum chemistry to diagnose hyperchloremic metabolic acidosis [176]. The long-term complications include anastomotic stricture (3%) and fistulae (6%) [177]. Another option is downward nephropexy and a long Boari flap. In cases of extensive ureteral loss or after multiple attempts at ureteral repair, the kidney can be relocated to the pelvis (auto-transplantation). The renal vessels are anastomosed to the iliac vessels and a ureteral re-implantation is performed [178, 179].

Buccal mucosa ureteroplasty is an option for long segment ureteral injury, especially after a previous failed reconstruction, as an alternative to auto-transplantation. The overall success rate is 90%, but experience is limited [180].

4.2.5.4 Permanent urinary diversion/nephrectomy

Following early or late repairs, up to 38% of patients develop secondary ureteric strictures requiring interventions [181] or palliative management by indwelling ureteric catheter or nephrostomy tube [164, 182]. Moreover, in some series up to 10% of failed repairs have evidence of renal parenchyma or function loss, leading to nephrectomy [164, 181].

Table 4.2.2: Principles of surgical repair of ureteral injury

Debridement of necrotic tissue
Spatulation of ureteral ends
Watertight tension-free mucosa-to-mucosa anastomosis using absorbable sutures
Internal stenting
External drain
Isolation of injury with peritoneum or omentum

4.2.6 *Summary of evidence and recommendations for the management of ureteral trauma*

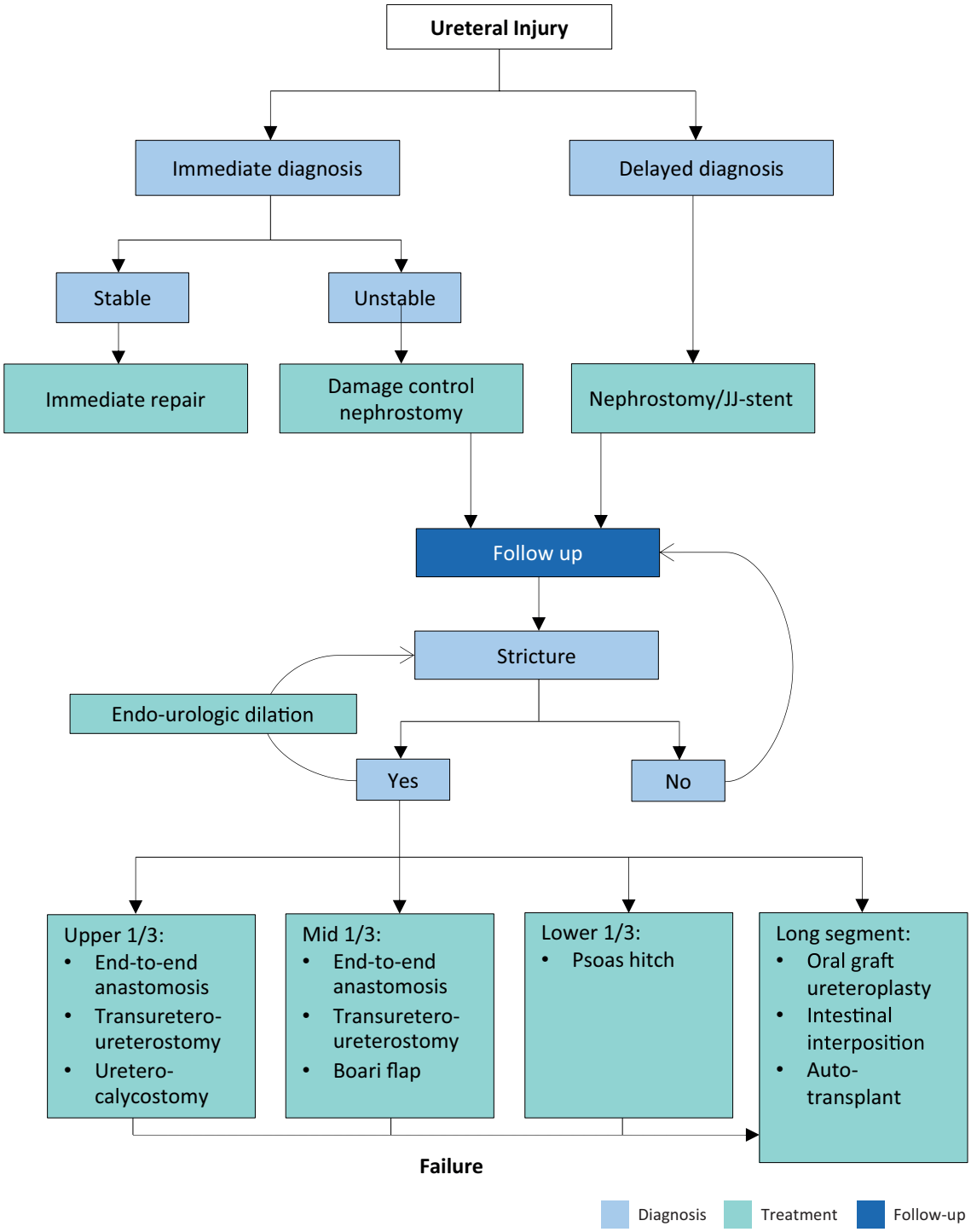
Summary of evidence	LE
Iatrogenic ureteral trauma is the most common cause of ureteral injury.	3
Gunshot wounds account for the majority of penetrating ureteral injuries, while road traffic accidents account for most blunt injuries.	3
Ureteral trauma usually accompanies severe abdominal and pelvic injuries.	3
Haematuria is an unreliable and poor indicator of ureteral injury.	3
Pre-operative prophylactic stents do not prevent ureteral injury; however, they may assist in its detection.	2
Endo-urological treatment of small ureteral fistulae and strictures is safe and effective.	3
Major ureteral injury requires ureteral reconstruction following temporary urinary diversion.	3

Recommendations	Strength rating
Visually identify the ureters to prevent ureteral trauma during complex abdominal and pelvic surgery.	Strong
Beware of concomitant ureteral injury in all abdominal penetrating trauma, and in deceleration-type blunt trauma.	Strong
Use pre-operative prophylactic stents in high-risk cases.	Strong
Repair iatrogenic ureteral injuries recognised during surgery immediately.	Strong
Treat iatrogenic ureteral injuries with delayed diagnosis by nephrostomy tube/JJ stent urinary diversion.	Strong
Manage ureteral strictures by ureteral reconstruction according to the location and length of the affected segment.	Strong

4.2.7 *Treatment algorithms*

Management of ureteral injuries

Figure 4.2.1: Management of ureteral injuries



4.3 Bladder Trauma

4.3.1 *Classification*

Bladder trauma is primarily classified according to the location of the injury: **intraperitoneal**, **extraperitoneal**, and **combined** intra-extraperitoneal [183], as it guides further management [184]. Bladder trauma is categorised by aetiology: **non-iatrogenic** (blunt and penetrating) and **iatrogenic** (external and internal).

4.3.2 *Epidemiology, aetiology, and pathophysiology*

Road traffic accidents (Motor vehicle accidents) are the most common cause of blunt bladder injury, followed by falls and other accidents. The main mechanisms are pelvic crush and blows to the lower abdomen [129, 183, 185]. Most patients with blunt bladder injury have associated pelvic fractures (60-90%) and other

intra-abdominal injuries (44-68.5%) [186, 187]. Pelvic fractures are associated with bladder injury in about 3% of cases [129, 188]; however, this can be as high as 26.5% in cases of severe pelvic injury [189]. Bladder injury is associated with urethral injury in 5-20% of cases [184, 187, 190].

The incidence of extraperitoneal (22.4-61.1%), and intraperitoneal (38.9-65.8%) injuries varies among series [191]. **Extraperitoneal injury** is almost always associated with pelvic fractures [185, 187]. It 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 contrecoup at the opposite side. The highest risk of bladder injury was found in disruptions of the pelvic circle with displacement > 1 cm, diastasis of the pubic symphysis > 1 cm, and pubic rami fractures [129, 184]. Occasionally, the bladder is directly perforated by a sharp bony fragment [184].

Intraperitoneal injury is caused by a sudden rise in intravesical pressure of a distended bladder, secondary to a blow to the pelvis or lower abdomen. The bladder dome is the weakest point of the bladder and ruptures usually occur there [184]. Penetrating injuries, mainly gunshot wounds, are rare except in conflict zones and violent urban areas [183, 192, 193]. Improvised explosive devices are the main cause of combat related bladder injuries in asymmetric warfare [194].

4.3.2.1 Iatrogenic bladder trauma (IBT)

The bladder is the urological organ that is most commonly affected by iatrogenic injury [195]. Table 4.3.1 shows the incidence of IBT during various procedures. **External IBT** occurs most often during obstetric and gynaecological procedures, followed by urological and general surgical operations [195]. Main risk factors are previous surgery, inflammation and malignancy [195]. Bladder perforations occur in up to 4.9% of mid-urethral sling operations for stress urinary incontinence in women. This rate is significantly lower in the obturator route compared to the retropubic route [196].

Internal IBT mainly occurs during transurethral resection of the bladder (TURB). Reported risk factors are larger tumours, older age, pre-treated bladders (previous TURB, intravesical instillations) and location at the bladder dome [197, 198]. Tumours at the lateral wall pose a risk factor because of the obturator jerk [199, 200]. Extraperitoneal perforations are more frequent than intraperitoneal perforations [198, 201], and perforations requiring intervention are rare (0.16-0.57%) [197].

Table 4.3.1: Incidence of iatrogenic bladder trauma during various procedures

Procedure	Percentage (%)
Obstetrics & Gynaecology	
Laparoscopic/Robotic radical hysterectomy (malignant) [202]	4.19-4.59
Abdominal radical hysterectomy (malignant) [202]	2.37
Hysterectomy laparoscopic/abdominal/vaginal (benign) [141, 203]	0.1-2.5
Caesarean delivery [204]	0.08-0.94
General surgery	
Abdominal cytoreductive surgery [205]	4.5
Rectal procedures [206]	0.27-0.41
Small/large bowel procedures [206]	0.12-0.14
Laparoscopic inguinal hernia repair [207]	0.04-0.14
Urology specific	
Transurethral resection of the bladder [208, 209]	3.5-58
Retropubic male sling [210]	8.0-19
Mid-urethral sling (retropubic route) [196, 211]	4.91-5.5
Transvaginal mesh surgery [212]	2.84
Pubovaginal sling [211]	2.8
Laparoscopic sacrocolpopexy [213]	1.9
Mid-urethral sling (transobturator route) [211]	1.61
Burch colposuspension [211, 214]	1.0-1.2
Native tissue colporrhaphy [212]	0.53

*4.3.3 **Diagnostic evaluation***

The principal sign of bladder injury is visible haematuria [184, 185]. Absolute indications for bladder imaging include: visible haematuria and a pelvic fracture [184] or non-visible haematuria combined with high-risk pelvic fracture (disruption of the pelvic circle with displacement > 1 cm or diastasis of the pubic symphysis > 1 cm) or posterior urethral injury [184]. Bladder trauma should also be suspected in patients with blunt urethral trauma and high Injury Severity Score (ISS) [215]. In the absence of these absolute indications, further imaging is based on clinical signs and symptoms including [184, 185, 192, 216]:

- inability to void or inadequate urine output;
- abdominal tenderness or distension due to urinary ascites, or signs of urinary ascites in abdominal imaging;
- uraemia and elevated creatinine level due to intraperitoneal re-absorption;
- entry/exit wounds at lower abdomen, perineum, or buttocks in penetrating injuries.

Intra-operative signs of external iatrogenic bladder injury include: extravasation of urine, visible laceration, visible bladder catheter, and blood and/or gas in the urine bag during laparoscopy [204]. Direct inspection is the most reliable method of assessing bladder integrity [195]. Retrograde bladder filling (with or without instillation of dye e.g., methylene blue) helps to detect smaller lesions [217, 218]. If bladder perforation is close to the trigone, the ureteric orifices should be inspected [195, 204].

Internal bladder injury is recognised by cystoscopic identification of fatty tissue, dark space, or bowel [208]. It may also be detected by the inability to distend the bladder, low return of irrigation fluid, or abdominal distension [219].

Post-operatively, missed bladder trauma is diagnosed by haematuria, abdominal pain, abdominal distension, ileus, peritonitis, sepsis, urine leakage from the wound, decreased urinary output, or increased serum creatinine [195, 204]. An IBT during hysterectomy or caesarean delivery can result in vesicovaginal or vesicouterine fistulae [204, 220].

4.3.3.1 Cystography

Cystography is the preferred diagnostic modality for non-iatrogenic bladder injury and for a suspected IBT in the post-operative setting [220, 221]. Both plain and CT cystography have a comparable sensitivity (90-95%) and specificity (100%) [185, 222]. However, CT cystography is superior in the identification of bony fragments in the bladder and bladder neck injuries, as well as concomitant abdominal injuries [184, 187].

Cystography must be performed using retrograde filling of the bladder with a minimum volume of 300-350 mL of dilute contrast material [221, 223]. Passive bladder filling by clamping the urinary catheter during the excretory phase of CT or IVP is not sufficient to exclude bladder injury [185]. Intraperitoneal extravasation is visualised by free contrast medium in the abdomen outlining bowel loops or abdominal viscera [224]. Extraperitoneal bladder injury is typically diagnosed by flame-shaped areas of contrast extravasation in the peri-vesical soft tissues. Contrast medium in the vagina is a sign of vesicovaginal fistula [220].

4.3.3.2 Cystoscopy

Cystoscopy is the preferred method for detection of intra-operative bladder injuries as it may directly visualise the laceration and 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 retropubic sub-urethral sling operations [196, 214]. Routine intra-operative cystoscopy during other gynaecologic procedures is not recommended [225], although the threshold to perform it should be low in any suspected bladder injury.

*4.3.4 **Prevention***

The risk of bladder injury is reduced by emptying the bladder by urethral catheterisation in every procedure where the bladder is at risk [217, 226]. Furthermore, the catheter's balloon can aid in identification of the bladder [217]. During TURB for tumours at the lateral wall, the incidence of internal IBT can be reduced by obturator nerve block or adequate muscle relaxation [200]. There is conflicting evidence whether bipolar TURB can reduce the risk for an obturator jerk [199, 200]. The use of combat pelvic protection systems reduces the risk of bladder and other genitourinary injuries due to the blast mechanism of improvised explosive devices [194, 227].

*4.3.5 **Disease management***

4.3.5.1 Conservative management

Conservative treatment, which comprises of clinical observation, continuous bladder drainage and antibiotic prophylaxis [198], is the standard treatment for an uncomplicated extraperitoneal injury due to blunt [184, 187, 190] or iatrogenic trauma [198].

Conservative treatment can also be chosen for uncomplicated intraperitoneal injury after TURB or other operations, but only in the absence of peritonitis and ileus [209, 224]. Placement of an intraperitoneal drain is advocated, especially when the lesion is larger [219, 228]. Penetrating extraperitoneal bladder injuries (only if minor and isolated) can also be managed conservatively [191, 216, 229].

4.3.5.2 Surgical management

Bladder closure is performed with absorbable sutures [191, 195]. There is no evidence that two-layer is superior to watertight single-layer closure [187, 191].

4.3.5.2.1 Blunt non-iatrogenic trauma

Most extraperitoneal ruptures can be treated conservatively; however, bladder neck involvement, bone fragments in the bladder wall, concomitant rectal or vaginal injury or entrapment of the bladder wall necessitate surgical intervention [184, 230]. There is an increasing trend to treat pelvic ring fractures with open stabilisation and internal fixation with osteosynthesis material. During this procedure, an extraperitoneal rupture should be sutured concomitantly in order to reduce the risk of infection [231]. Likewise, an extraperitoneal rupture should be sutured during surgical exploration for other injuries, in order to decrease the risk of complications and to reduce recovery time [190]. In case of extraperitoneal injury with pelvic fractures treated by internal fixation, there is conflicting evidence about the need to repair the bladder in order to reduce the risk of infection [231, 232].

Intraperitoneal ruptures should always be managed by surgical repair [184, 187] because intraperitoneal urine extravasation can lead to peritonitis, intra-abdominal sepsis and death [186]. Abdominal organs should be inspected for possible associated injuries and urinomas must be drained if detected. Laparoscopic suturing of the intraperitoneal rupture is also possible [185].

4.3.5.2.2 Penetrating non-iatrogenic trauma

Penetrating bladder injury is managed by emergency exploration, debridement of devitalised bladder wall and primary bladder repair [192, 193]. A midline exploratory cystotomy is advised to inspect the bladder wall and the distal ureters [191, 192]. In gunshot wounds, there is a strong association with intestinal and rectal injuries, usually requiring faecal diversion [192, 216]. Most gunshot wounds are associated with two transmural injuries (entry and exit wounds) and the bladder should be carefully checked for these two lesions [192]. As the penetrating agent (bullet, knife) is not sterile, antibiotic treatment is advised [193]. In selected patients (haemodynamically stable without associated injuries), penetrating well-contained extraperitoneal bladder injuries probably can be safely managed non-operatively [233].

4.3.5.2.3 Iatrogenic bladder trauma

Perforations lacerations intra-operatively are primarily closed [234]. Bladder injuries not recognised during surgery or internal IBT should be managed according to their location. The standard of care for intraperitoneal injuries is surgical exploration and repair [224]. If surgical exploration is performed after TURB, the bowel must be inspected to rule out concomitant injury [197]. For extraperitoneal injuries, exploration is only needed for perforations complicated by symptomatic extravesical collections. It requires drainage of the collection, with or without closure of the perforation [235]. If bladder perforation is encountered during mid-urethral sling or transvaginal mesh procedures, sling re-insertion and urethral catheterisation (two to seven days) should be performed [236].

*4.3.6 **Follow-up***

Continuous bladder drainage is required to prevent elevated intravesical pressure and to allow the bladder to heal [195, 237]. Conservatively treated bladder injuries (traumatic or external IBT) are followed up by cystography to rule out extravasation and ensure proper bladder healing [184]. The first cystography is planned approximately ten days after injury [191]. In case of ongoing leakage, cystoscopy should be performed to rule out bony fragments in the bladder, and a second cystography is warranted one week later [184].

After operative repair of a simple injury in a healthy patient, the catheter can be removed after five to ten days without cystography [237, 238]. In cases of complex injury (trigone involvement, ureteric re-implantation) or risk factors of impaired wound healing (e.g., steroids, malnutrition) cystography is advised [191, 237]. For conservatively treated internal IBT, catheter drainage, lasting five to seven days, is proposed [198, 201].

4.3.7 Summary of evidence and recommendations for bladder injury

Summary of evidence	LE
The combination of pelvic fracture and visible haematuria is highly suggestive of bladder injury.	3
Cystography is the preferred diagnostic modality for non-iatrogenic bladder injury and for suspected IBT in the post-operative setting.	3
Cystography must be performed using retrograde filling of the bladder with a minimum volume of 300-350 mL of dilute contrast material. Passive bladder filling by clamping the urinary catheter during the excretory phase of CT or IVP is not sufficient to exclude bladder injury.	3
The risk of bladder perforation during mid-urethral sling operations for stress urinary incontinence is lower for the obturator route compared to the retropubic route.	1a
Conservative treatment, which comprises of clinical observation, continuous bladder drainage and antibiotic prophylaxis, is the standard treatment for an uncomplicated extraperitoneal injury due to blunt trauma.	3
In extraperitoneal bladder injury with either bladder neck involvement, bone fragments in the bladder wall, concomitant rectal or vaginal injury, or entrapment of the bladder wall, surgical intervention is necessary in order to decrease the risk of complications and to reduce recovery time.	3
Intraperitoneal bladder trauma is managed by surgical repair because intraperitoneal urine extravasation can lead to peritonitis, intra-abdominal sepsis, and death.	3
Conservative treatment is suitable for uncomplicated intraperitoneal injury during endo-urological procedures, in the absence of peritonitis and ileus.	3
In cases of complex injury (trigone involvement, ureteric re-implantation) or risk factors of impaired wound healing (e.g., steroids, malnutrition) cystography is advised after bladder repair.	2a

Recommendations	Strength rating
Perform cystography in the presence of visible haematuria and pelvic fracture.	Strong
Perform cystography in case of suspected iatrogenic bladder injury in the post-operative setting.	Strong
Perform cystography with active retrograde filling of the bladder with dilute contrast (300-350 mL).	Strong
Perform cystoscopy to rule out bladder injury during retropubic sub-urethral sling procedures.	Strong
Manage uncomplicated blunt extraperitoneal bladder injuries conservatively.	Weak
Manage blunt extraperitoneal bladder injuries operatively in cases of bladder neck involvement and/or associated injuries that require surgical intervention.	Strong
Manage blunt intraperitoneal injuries by surgical exploration and repair.	Strong
Manage small uncomplicated intraperitoneal bladder injuries during endoscopic procedures conservatively.	Weak
Perform cystography to assess bladder wall healing after repair of a complex injury or in case of risk factors for wound healing.	Strong

4.4 Urethral Trauma

4.4.1 Epidemiology, aetiology and pathophysiology

4.4.1.1 Anterior male urethral injury

The bulbar urethra is the most common site affected by blunt trauma. In bulbar injuries, the bulb is compressed against the pubic symphysis, resulting in rupture of the urethra at the site of compression [239]. Possible mechanisms are straddle injuries or kicks to the perineum. A penile fracture can be complicated by a urethral injury in approximately 15% of cases [240, 241]. **Penetrating** anterior injuries are rare and are usually caused by gunshot wounds, stab wounds, dog bites, impalement, or penile amputations [239]. Depending on the affected segment, penetrating injuries are usually associated with penile, testicular and/or pelvic injuries [242]. 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 [243].

Iatrogenic injury is the most common type of urethral trauma [244]. The incidence of male urethral injury during transurethral catheterisation is 13.4 per 1,000 catheters inserted [245]. Injuries can occur due to creation of a false passage by the tip of the catheter or inadvertent inflation of the anchoring balloon in the urethra [245]. The importance of catheter insertion training programmes [246, 247] and the implementation of difficult urinary catheterisation protocols [248], to prevent urethral injury during transurethral catheterisation, have been demonstrated. Preliminary data suggests that guidewire led catheter insertion, or use of a safety valve for balloon inflation may prevent urethral trauma in difficult catheterisation cases [249, 250]. A SR of the use of hydrophilic coated catheters, in patients performing intermittent catheterization, showed no clear benefit [251].

During penile prosthesis insertion, the risk of urethral perforation is 0.1-4%. Proximal urethral injuries are more common than distal ones [252].

4.4.1.2 Posterior male urethral injuries

Blunt posterior urethral injuries are almost exclusively related to pelvic fractures and the risk increases with fracture configuration severity [253]. These injuries are referred to as pelvic fracture urethral injuries (PFUI) [239], and are mainly caused by road traffic accidents [254]. Pelvic fracture urethral injuries are divided into partial or complete ruptures [253, 254]. In complete ruptures, there is a gap between the disrupted ends of the urethra, which fills up with scar tissue. There is no urethral wall in the scarred space and any lumen represents a fistulous tract between the urethral stumps [255]. Injuries of the bladder neck and prostate are rare and mostly occur at the anterior midline of both the bladder neck and prostatic urethra [256]. It is highly uncommon to find a complete transection of the bladder neck or an avulsion of the anterior part of the prostate [256]. Concomitant injuries to the head, thorax, abdomen and/or spine are frequent (up to 66%) [254].

Penetrating injuries of the pelvis, perineum, or buttocks (mainly gunshot wounds) can also damage the posterior urethra but are extremely rare in the civilian setting [253]. There is a high probability of associated injuries (approx. 90%), mainly intra-abdominal [192].

The associated injuries which occur with both blunt and penetrating posterior urethral injuries can be life-threatening, and if so, will govern the patient's assessment and treatment [254]. Delayed morbidities of posterior urethral injuries include strictures, incontinence and erectile dysfunction, all of which may have a detrimental effect on the patient's quality of life [257]. The pooled estimate for the proportion of patients with erectile dysfunction following PIFU is 34% [258].

Iatrogenic injury has been reported with transanal total mesorectal excision in 1-11% of cases. This injury is usually partial and located at the membranous urethra [259].

4.4.1.3 Female urethral injuries

Birth related injuries to the female urethra are rare and consist of minor (peri)urethral lacerations during vaginal delivery. Pelvic fractures are the main cause of **blunt** trauma [260]; however, PFUIs in females are rare and less common than in males [253]. This is usually attributed to the flexibility provided by the vagina and the greater inherent elasticity of the female urethra [260], it may also be the result of less severe and more frequent stable pelvic fractures in females [184, 254]. In unstable pelvic fractures in females, a high suspicion for a urethral injury should be maintained [260]. Female urethral injuries are classified into two types: longitudinal or partial (most frequent) injuries and transverse or complete injuries [260]. Concomitant bladder or vaginal injury is possible; therefore, females are at risk of developing urinary incontinence and urethrovaginal fistula [254, 260].

Insertion of a synthetic sub-urethral sling for the treatment of female stress urinary incontinence is complicated by an intra-operative urethral injury in 0.2-2.5% of cases [261] and is an important cause of **iatrogenic** urethral injury.

*4.4.2 **Evaluation***

4.4.2.1 Clinical signs

Blood at the meatus is the cardinal sign, but the absence of it doesn't rule out a urethral injury [184, 254]. Inability to void (with a palpable distended bladder) is another classic sign and is often associated with a complete rupture [254, 255]. Haematuria and pain on urination may be present in incomplete ruptures. Urinary extravasation and bleeding may result in scrotal, penile and/or perineal swelling and ecchymosis, depending on the location and extent of the trauma. The presentation of these clinical symptoms may be delayed (> 1 hour) [255].

Rectal examination should always be done to exclude an associated rectal injury (up to 5% of cases) and may reveal a 'high-riding' prostate, which is an unreliable finding [184, 255]. Failure to detect a rectal injury can cause significant morbidity and even mortality. A rectal injury is suggested by blood on the examining finger and/or a palpable laceration [184]. Another sign of urethral injury is difficulty or inability to pass a urethral catheter [184, 255].

A female urethral injury should be suspected from the combination of a (unstable) pelvic fracture with blood at the vaginal introitus, vaginal laceration, haematuria, urethrorrhagia, labial swelling, urinary retention, or difficulties passing a urethral catheter [184, 257]. Vaginal examination is indicated to assess vaginal lacerations [184, 257].

4.4.2.2 Urethrography

Retrograde urethrography (RUG) is the standard in the early evaluation of a male urethral injury [184, 262] and is conducted by injecting 20-30 mL of contrast material while occluding the meatus. Films should be taken in a 30° oblique position. In patients with PFUI, it is important to move the X-ray beam to the 30° angle rather than the patient [254]. In an unstable patient, RUG should be postponed until the patient has been stabilised [184, 192].

During RUG, any extravasation outside the urethra is pathognomonic for urethral injury [255]. 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 [254]. Although RUG is able to reliably identify the site of injury (anterior vs. posterior), the distinction between a complete and partial rupture is not always clear [254, 263]. Therefore, any proposed classification system based on RUG is not reliable [254, 263]. In females, the short urethra and vulvar oedema makes adequate urethrography nearly impossible [264].

Prior to deferred treatment, a combination of RUG and antegrade cysto-urethrography is the standard to evaluate site and extent of the urethral stenosis, and to evaluate the competence of the bladder neck [254].

4.4.2.3 Cysto-urethroscopy

Flexible cysto-urethroscopy is a valuable alternative to diagnose an acute urethral injury and may distinguish between complete and partial rupture [262]. Flexible cysto-urethroscopy is preferred to RUG in suspected penile fracture-associated urethral injury as RUG is associated with a high false-negative rate [265, 266]. In females, where the short urethra often precludes adequate radiological visualisation, cysto-urethroscopy and vaginoscopy are the diagnostic modalities of choice [184, 260]. If, prior to deferred treatment, the competence of the bladder neck is not clear upon antegrade cysto-urethrography, a suprapubic cystoscopy is advised [254].

4.4.2.4 Ultrasound and magnetic resonance imaging

In the acute phase, US scanning is used for guiding the placement of a suprapubic catheter [254]. In complex PFUIs, MRI before deferred treatment provides valuable additional information, which can help to determine the most appropriate surgical strategy [267]. This information includes a better estimation of the length of the distraction defect, degree of prostatic displacement and presence/absence of a false passage [267].

*4.4.3 **Disease Management***

4.4.3.1 Male anterior urethral injuries

4.4.3.1.1 Immediate exploration and urethral reconstruction

This is indicated for penile fracture related injuries [268] and non-life-threatening penetrating injuries [257]. Small lacerations can be repaired by simple closure [241]. Complete ruptures without extensive tissue loss are treated with anastomotic repair [241, 242]. Only 2% of cases will develop a urethral stricture after immediate urethral reconstruction for penile fracture [268]. In the case of longer defects or apparent infection (particularly bite wounds), a staged repair with urethral marsupialisation is needed [262]. Penetrating injuries require peri- and post-operative antibiotic treatment [269].

Immediate urethroplasty has been performed in blunt injuries. The long term-outcomes (patency rate, potency rate) of patients treated with immediate urethroplasty is similar to these initially treated with suprapubic diversion and delayed urethroplasty [270]. The main advantage of performing immediate urethroplasty is that this strategy significantly reduces the time to spontaneous voiding from two to six months to three weeks on average [270, 271]. Spongiosal contusion and haematoma during immediate urethroplasty will make the operation technically more demanding; therefore, immediate urethroplasty should be performed by a dedicated urethral surgeon [271].

Perforation of the distal urethra during penile prosthesis insertion needs to be repaired over a catheter; in this instance the initial procedure should be abandoned [272].

4.4.3.1.2 Urinary diversion

Blunt anterior urethral injuries are associated with spongiosal contusion. Evaluation of the limits of urethral debridement in the acute phase might be difficult and as a consequence, it is reasonable to start with urinary diversion only [262].

If urinary diversion is performed, the therapeutic options are suprapubic diversion or a trial of early endoscopic re-alignment with transurethral catheterisation [262]; there is conflicting evidence as to which intervention is superior [270, 271, 273]. A retrospective case series of 44 patients comparing early realignment versus suprapubic tube placement, shows no difference in stricture formation [274].

Urinary diversion is maintained for one to two weeks for partial ruptures and three weeks for complete ruptures [262, 273]. A review of 49 Chinese studies (1,015 patients), reported a 57% (range: 0 - 100%) success rate for endoscopic re-alignment of blunt anterior injuries [270]. The wide range in success rate most likely reflects a mix of partial and complete ruptures which was not further specified in the review. For complete ruptures, urinary diversion on its own is unlikely to result in a successful outcome (0 - 25% patency rate) [271, 273].

Transurethral or suprapubic urinary diversion are treatment options for iatrogenic or life-threatening penetrating injuries [257, 275]. Minor iatrogenic urethral injuries and urethral contusions do not require urinary diversion [3].

4.4.3.2 Male posterior urethral injuries

4.4.3.2.1 Emergency room management

As these injuries are usually associated with other severe injuries, resuscitation and immediate treatment of life-threatening injuries have absolute priority [254]. Penetrating injuries especially have a very high likelihood of associated injuries requiring immediate exploration [192, 276]. There is no urgency to treat the urethral injury and urinary diversion is not essential during the first hours after trauma [255]; however, it is preferable to establish early urinary diversion to:

- monitor urinary output, since this is a valuable sign of the haemodynamic condition and the renal function of the patient;
- treat symptomatic retention if the patient is still conscious;
- minimise urinary extravasation and its secondary effects, such as infection and fibrosis [254].

Insertion of a suprapubic catheter is an accepted practice in urgent situations [255, 276]. However, insertion of a suprapubic catheter is not without risk, especially in the unstable trauma patient where the bladder is often displaced by a 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 personnel. It is extremely unlikely that the gentle passage of a urethral catheter will do any additional damage [254]. If there is any difficulty, a suprapubic catheter should be placed under US guidance or under direct vision, for example, during laparotomy for associated injuries [254]. Suprapubic catheter placement does not increase the risk of infectious complications in patients undergoing internal fixation to stabilise a pelvic fracture [277]. Therefore, the assertion that suprapubic catheter placement would increase the risk of orthopaedic hardware infection and subsequent explantation is not justified [277].

4.4.3.2.2 Early urethral management (less than six weeks after injury)

For partial injuries, urinary diversion (suprapubic or transurethral) is sufficient as these injuries can heal without significant scarring or obstruction [255, 257]. A complete injury will not heal, and formation of an obliterated segment is inevitable in case of suprapubic diversion alone [255, 257]. To avoid this obliteration and a long period of suprapubic diversion followed by deferred urethroplasty, the urethral ends can be sutured (urethroplasty) or approximated over a transurethral catheter (re-alignment).

4.4.3.2.2.1 Early re-alignment

Early re-alignment can be performed when a stable patient is on the operating table for other surgery or as a stand-alone procedure in the absence of concomitant injuries [192, 278]. In a partial injury, re-alignment, and transurethral catheterisation avoids extravasation of urine in the surrounding tissues reducing the inflammatory response. In complete injuries, the aim of re-alignment is to correct severe distraction injuries rather than to prevent a stricture [257, 279].

Re-alignment can be done by an open or endoscopic technique [279, 280]. The open technique is associated with longer operation times, more blood loss and longer hospital stays; as such, endoscopic re-alignment is now preferred [270]. Using a flexible/rigid cystoscope and biplanar fluoroscopy, a guidewire is placed inside the bladder under direct visual control, over this, a catheter is placed. If necessary, two cystoscopes can be used: one retrograde (per urethra) and one antegrade (suprapubic route through the bladder neck) [254]. The duration of catheterisation is three weeks for partial and six weeks for complete ruptures with voiding urethrography upon catheter removal [254]. It is important to avoid traction on the balloon catheter as it can damage the remaining sphincter mechanism at the bladder neck [254].

With contemporary endoscopic re-alignment procedures, stricture formation is reduced to 44-49% [279, 280] compared to a 89-94% stricture rate with suprapubic diversion [280, 281]. There is no evidence that early re-alignment increases the risk of urinary incontinence (4.7-5.8%) or erectile dysfunction (16.7-20.5%) [280, 281].

Another potential benefit of early re-alignment is that when a stricture occurs it will be shorter and therefore, easier to treat. For short, non-obliterative strictures following re-alignment, direct vision urethrotomy can be performed. Approximately 50% of strictures after endoscopic re-alignment can be treated endoscopically [279]. However, repetitive endoscopic procedures in case of stricture formation might delay the time to definitive cure and can increase the incidence of adverse events (false passage, abscess formation) [282, 283]. In light of this, repetitive endoscopic treatments after failed re-alignment are not recommended; instead, urethroplasty must be performed.

A retrospective review found a shorter stricture length after early (open) re-alignment and as a consequence, a tendency for less complex manoeuvres to be needed to allow for a tension-free anastomosis during urethroplasty [284]. On the other hand, another retrospective review, reported an equal stricture length and no greater facilitation of urethroplasty after failed endoscopic re-alignment compared to suprapubic diversion only [282]. The proposed benefit is thus highly questionable. Furthermore, there is conflicting evidence as to whether failed early re-alignment jeopardises the success of definitive urethroplasty [254].

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 [184, 279].

4.4.3.2.2.2 Early urethroplasty

Immediate urethroplasty within 48 hours after injury is difficult because of poor visualisation and the inability to accurately assess the degree of urethral disruption, due to extensive swelling and ecchymosis, which may result in extensive unjustified urethral debridement. Another problem is the risk of severe bleeding (average 3 L) following entry into the pelvic haematoma [254]. In addition, with high rates of impotence (23%), incontinence (14%) and strictures (54%), urethroplasty within 48-hours is not indicated [254].

Early urethroplasty can be performed after two days and up to six weeks after the initial injury, if associated injuries have been stabilised, the distraction defect is short, the perineum is soft and the patient is able to lie down in the lithotomy position [285, 286]. This avoids a long period of suprapubic diversion with its discomfort and complications [285, 286]. As the results (complications, stricture recurrence, incontinence, and impotence) are equivalent to delayed urethroplasty [286-288], early urethroplasty might be an option for patients fulfilling the above-mentioned criteria.

Lacerations (blunt or penetrating) at the bladder neck and prostatic urethra are a specific entity: they will never heal spontaneously, will cause local cavitation (presenting a source of infection) and compromise the intrinsic sphincter mechanism (with increased risk of urinary incontinence) [256]. They must be reconstructed as soon as possible [257, 263, 276]. For penetrating injuries with severe lesions to the prostate, prostatectomy (bladder neck sparing) must be performed [276].

4.4.3.2.3 Deferred management (greater than three months after injury)

The standard treatment remains deferred urethroplasty [13, 14]. 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 [255]. Endoscopic treatment of a complete obliteration is not successful [254]. After at least three months of suprapubic diversion, the pelvic haematoma is nearly always resolved, the prostate has descended into a more normal position, the scar tissue has stabilised [285] and the patient is clinically stable and able to lie down in the lithotomy position [262, 285]. Associated life-threatening injuries often preclude early management of penetrating membranous urethral injuries. In those cases, suprapubic diversion with delayed urethroplasty is also advised [17, 25, 27]. Perineal anastomotic repair is the surgical technique of choice, but a combined abdominoperineal approach is necessary in rare cases of concomitant bladder neck injury or recto-urethral fistula [289].

An extensive overview of deferred urethroplasty can be found in the Urethral Strictures Guidelines [290].

4.4.3.2.4 Iatrogenic posterior injuries

Urethral defects during transanal total mesorectal excision were repaired by direct suture repair via a transperineal approach in a small case series (n=32). Despite direct repair, 26% developed complications including urethral stricture, urethral dehiscence, recto-urethral fistula, and recto-perineal fistula. No evidence on other strategies is available [259].

4.4.3.3 Female urethral injuries

Emergency room management of PFUIs in females is the same as in males (section 4.4.3.2.1); however, subsequent management differs. Treatment options are [260]:

- **Early realignment:** This is associated with a high stricture and fistula rate.
- **Early repair (less than or equal to seven days):** Complication rate is the lowest with early repair; therefore, this strategy is preferred once the patient is haemodynamically stable [257, 260].
- **Delayed repair (greater than seven days):** Delayed repair often requires complex abdominal or combined abdominal-vaginal reconstruction with elevated risk of urinary incontinence and vaginal stenosis.

The approach (vaginal, abdominal or combined) for early repair depends on the location of the injury [260]. 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 or urethral laceration. Concomitant vaginal lacerations are repaired (two-layer closure) trans vaginally at the same time [260]. Distal urethral injuries can be left hypospadiac since they do not disrupt the sphincter mechanism, but a concomitant vaginal laceration must be closed [184, 264]. In case of urethral injury during synthetic sub-urethral sling insertion, immediate repair is warranted with abandonment of sling insertion [261].

Table 4.4.1: Complication rates for different treatment strategies for PFUIs in females [260]

Type of repair	Stricture (%)	Fistula (%)	Incontinence (%)	Vaginal stenosis (%)	Need for permanent urinary diversion (%)
Early realignment	59	13	0	0	0
Early repair	3	6	9	0	3
Delayed repair	3	4	31	4	7

4.4.4 Summary of evidence and recommendations for the evaluation and management of urethral trauma

Summary of evidence	LE
Implementing training programmes on urinary catheter insertion for personnel involved with urethral catheterisation significantly improves the rate of catheter-related complications.	2b
In males, a urethral injury is detected as contrast extravasation during urethrography or as a mucosal laceration during cysto-urethroscopy.	3
As opposed to cysto-urethroscopy, voiding cysto-urethrography will miss a female urethral injury in approximately 50% of cases.	3
Transurethral or suprapubic urinary diversion are the treatment options for iatrogenic injuries.	3
With urinary diversion (suprapubic or transurethral catheter) satisfactory urethral luminal re-canalisation may occur after partial blunt anterior urethral ruptures.	3
Complete blunt anterior urethral ruptures are unlikely to be cured by urinary diversion alone, whereas immediate urethroplasty has an equal success rate compared to delayed urethroplasty. The main advantage of immediate urethroplasty is to reduce the time to spontaneous voiding.	3
If PFUIs are associated with life-threatening injuries, urethral management has no priority and urinary diversion with either urethral or suprapubic catheterisation is sufficient initially.	3
With early endoscopic re-alignment the stricture rate is reduced to 44-49% without increased risk of incontinence or erectile dysfunction.	3
Repetitive endoscopic treatments after failed re-alignment delay the time to definitive cure and increase the incidence of adverse events.	3
For partial posterior injuries, urinary diversion (suprapubic or transurethral) is sufficient as these injuries might heal without significant scarring or obstruction.	3

Immediate urethroplasty (< 48 hours) in male PFUI is associated with a higher risk of bleeding, stricture, incontinence, and impotence rates compared to delayed urethroplasty.	3
In selected patients for male PFUI, early urethroplasty (two days to six weeks) is associated with similar stricture, incontinence and impotence rates compared to delayed urethroplasty.	3
Suprapubic diversion with delayed urethroplasty in male PFUI with complete urethral disruption is associated with an 86% stricture free success rate and with no significant impact on erectile function and urinary continence.	2a
Early repair in female PFUI has the lowest complication rate.	3

Recommendations	**Strength rating**
Provide appropriate training to reduce the risk of traumatic catheterisation.	Strong
Evaluate male urethral injuries with flexible cysto-urethroscopy and/or retrograde urethrography.	Strong
Evaluate female urethral injuries with cysto-urethroscopy and vaginoscopy.	Strong
Treat iatrogenic anterior urethral injuries by transurethral or suprapubic urinary diversion.	Strong
Treat partial blunt anterior urethral injuries by suprapubic or urethral catheterisation.	Strong
Treat complete blunt anterior urethral injuries by immediate urethroplasty, if surgical expertise is available, otherwise perform suprapubic diversion with delayed urethroplasty.	Weak
Treat pelvic fracture urethral injuries (PFUIs) in haemodynamically unstable patients by transurethral or suprapubic catheterisation initially.	Strong
Perform early endoscopic re-alignment in male PFUIs when feasible.	Weak
Do not repeat endoscopic treatments after failed re-alignment for male PFUI.	Strong
Treat partial posterior urethral injuries initially by suprapubic or transurethral catheter.	Strong
Do not perform immediate urethroplasty (< 48 hours) in male PFUIs.	Strong
Perform early urethroplasty (two days to six weeks) for male PFUIs with complete disruption in selected patients (stable, short gap, soft perineum, lithotomy position possible).	Weak
Manage complete posterior urethral disruption in male PFUIs with suprapubic diversion and deferred (at least three months) urethroplasty.	Strong
Perform early repair (within seven days) for female PFUIs (not delayed repair or early re-alignment).	Strong

*4.4.5 **Treatment algorithms***

Management of anterior and posterior urethral injuries in men

Figure 4.4.1: Management of anterior urethral injuries in men

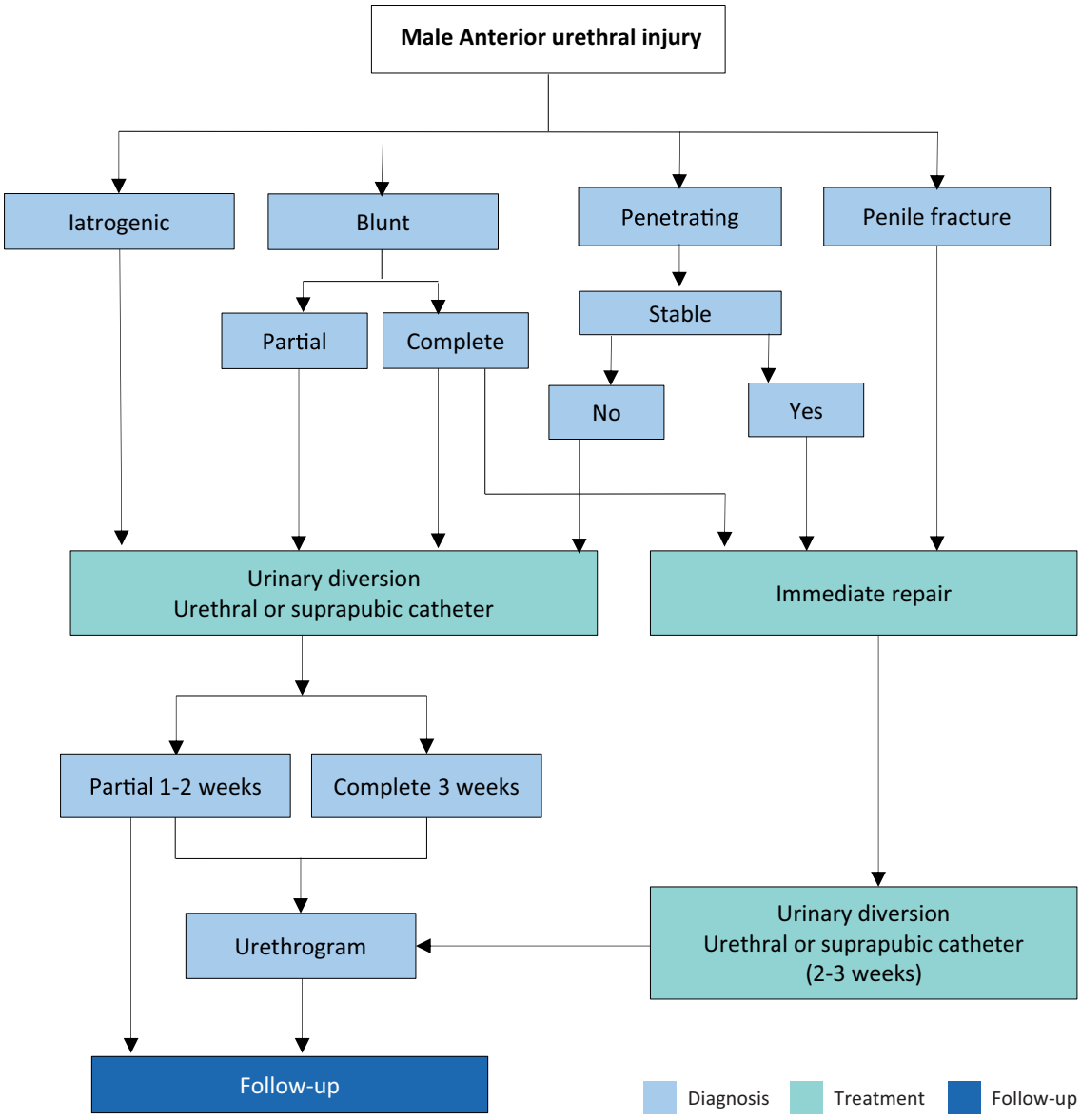
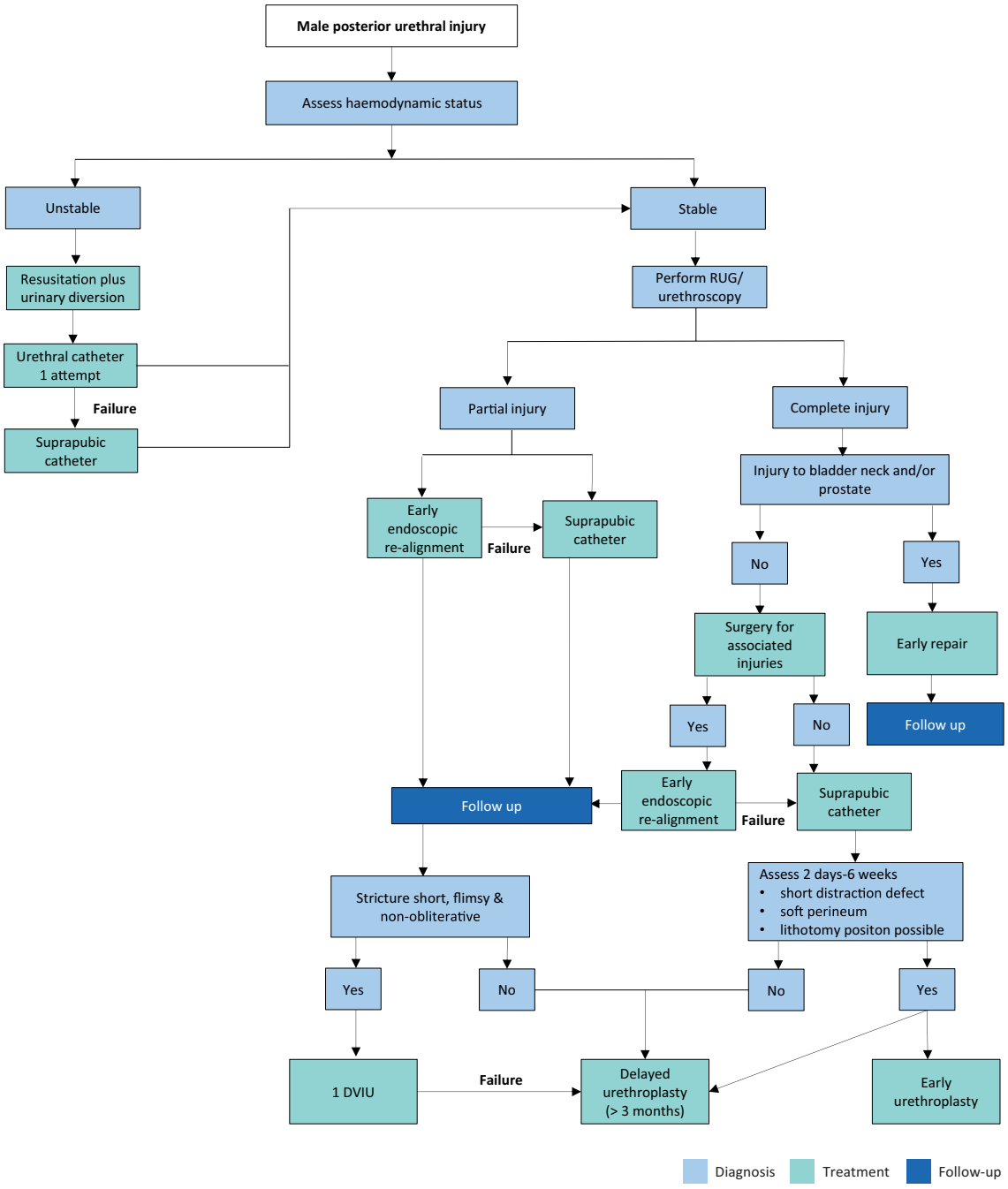


Figure 4.4.2: Management of posterior urethral injuries in men



RUG = retrograde urethrography; DVIU = direct visual internal urethrotomy.

4.5 Genital Trauma

4.5.1 Epidemiology, aetiology and pathophysiology

Of all urological injuries, 33-66% involve the external genitalia [291]. 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 crime [292]. The risk of associated injuries to neighbouring organs (bladder, urethra, vagina, rectum, and bowel), after blunt trauma is higher in females than in males.

Genital trauma is commonly caused by blunt injuries (80%). In males, blunt genital trauma frequently occurs unilaterally with approximately 1% presenting as bilateral scrotal or testicular injuries [293]. Any kind of contact sport, without the use of protective aids, may be associated with genital trauma. Off-road cycling, motor biking (especially on motorbikes with a dominant petrol tank), rugby, football and hockey are all activities associated with blunt testicular trauma [294-297]. Penetrating injuries are most commonly caused by firearms (75.8%) with the majority requiring surgical intervention [298, 299].

Accidents during sexual intercourse can also cause genital trauma; men of younger age are the most affected. The major pathologies are penile fractures, strangulation, necrosis, and assorted injuries from various sexual practices [300, 301].

The most important presentation of blunt penile trauma is penile fracture. The most common causes are sexual intercourse, forced flexion (taqaandan), masturbation and rolling over in 46%, 21%, 18% and 8.2%, respectively [302]. It has also been reported that penile fracture patients have a significantly higher rate of substance abuse [303]. The usual 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 [304], with penile fracture more likely in certain positions [305]. 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% [306-308]. Genital injury is prevalent (42%) after sexual abuse [309].

Although animal bites are common, bites injuring the external genitalia are rare. Wounds are usually minor but have a risk of wound infection.

Gunshot injuries to the external genitalia are relatively uncommon and are usually not life-threatening; however, they can have a significant impact on quality of life. About 40-60% of all penetrating genito-urinary lesions involve the external genitalia [310, 311], 35% of these are gunshot wounds [293]. In a series of wartime injuries, the majority were caused by improvised explosive devices and other explosive ordinance, while smaller numbers of injuries were due to gunshot injuries [312]. In both males and females, penetrating injuries affect multiple organs in 70% of patients. In males, penetrating scrotal injuries affect both testes in 30% of cases compared with 1% in blunt injuries [293, 313]. Self-mutilation of the external genitalia has also been reported in psychotic patients and transsexuals [314]. Genital burns are rare in isolation and are usually due to industrial flames or chemicals [315]. Both male and female genital piercings increase the risk for unexpected genital trauma [316].

Traumatic dislocation of the testicle rarely occurs and is most common in victims of road traffic accidents [317-320]. Bilateral dislocation of the testes has been reported in up to 25% of cases [318]. Testicular rupture is found in approximately 50% of cases of direct blunt scrotal trauma [321, 322]. It may occur under intense compression of the testis against the inferior pubic ramus or symphysis, resulting in a rupture of the tunica albuginea. A force of approximately 50 kg is necessary to cause testicular rupture [323]. Most penile avulsion injuries are self-inflicted, but some are a result of industrial accidents or assault.

Coital injury of the female genital tract can happen during consensual sexual intercourse. Up to 35% of all genital injuries in women are sustained during their first sexual contact. The most frequently found injuries are lacerations [324]. 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 one in 310 deliveries [325]. The presence of a vulvar haematoma is closely related to an increased risk of associated vaginal, pelvic, or abdominal injuries [326, 327]. Blunt injuries of the vulva and vagina are associated with pelvic trauma in 30%, after consensual intercourse in 25%, following sexual assault in 20%, and other blunt trauma in 15% [328].

*4.5.2 **Diagnostic evaluation***

4.5.2.1 Patient history and physical examination

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 [240]. 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 [302].

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. **Blunt vulvar** or perineal trauma in women may be associated with bleeding, pain and voiding problems, bladder catheterisation is usually required.

In genital trauma, a urinalysis should be performed. The presence of visible haematuria requires a retrograde urethrogram in males. In females, flexible or rigid cystoscopy is recommended to exclude urethral and bladder injury [326, 328]. In women with genital injuries and blood at the vaginal introitus, further gynaecological investigation is needed [326].

*4.5.3 **Imaging***

In cases of suspected penile fracture cavernosography, US or contrast-enhanced MRI [302, 329-331] can identify lacerations of the tunica albuginea in unclear cases [332], or provide reassurance that the tunica is intact. Magnetic resonance imaging is superior to US in diagnosing penile fracture [333, 334]. If a concomitant urethral injury is suspected, manage as outlined in section 4.4.

Ultrasound should be performed to determine intra- and/or extra-testicular haematoma, testicular contusion, or rupture [322, 335-343]. However, the literature is contradictory as to the usefulness of US compared to clinical examination alone. Some studies have reported convincing findings with a specificity of up to 98.6% [344]. Heterogeneous echo pattern of the testicular parenchyma with the loss of contour definition is a highly sensitive and specific radiographic finding for testicular rupture [333]. Others reported poor specificity (78%) and sensitivity (28%) for the differentiation between testicular rupture and haematocele, while accuracy is as low as 56% [336]. 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 [345]; however, these techniques did not specifically increase the detection rates of testicular rupture [346].

*4.5.4 **Disease management***

4.5.4.1 Animal bites

Local wound management depends on the extent of tissue destruction. Antibiotics should be prescribed in accordance with local resistance patterns [347-349]. The possibility of rabies infection must be considered, taking into account the geographical location, animal involved, specific nature of the wound and the type of attack (provoked/unprovoked). Elderly and immunosuppressed patients should be vaccinated with human rabies immunoglobulin and human diploid cell vaccine [350, 351].

4.5.4.2 Human bites

In cases of human bites, apart from wound management, infection should be considered since transmission of viral diseases may occur, 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 [352].

4.5.4.3 Blunt penile trauma

Blunt trauma to the flaccid penis does not usually cause tearing of the tunica. Subcutaneous haematoma after sexual intercourse, without associated rupture of the cavernosal tunica albuginea, does not require surgical intervention. In these cases, non-steroidal analgesics and ice-packs are recommended [353].

4.5.4.4 Penile fracture

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 [344, 354]. When a penile fracture is diagnosed, surgical intervention with closure of the tunica albuginea is recommended; it ensures the lowest rate of negative long-term sequelae and has no negative effect on the psychological wellbeing of the patient [355]. The approach is usually through a circumferential incision proximal to the coronal sulcus which enables complete degloving of the penis. Increasingly, local longitudinal incisions centred on the area of fracture or ventral longitudinal approaches are currently used [265]. A recent systematic review on the management of penile fractures concluded that immediate repair should be within 24 hours of presentation [356]; however, delayed presentation should not prevent exploration [305]. Further localisation may be gained with a flexible cystoscopy performed prior to incision, if urethral trauma is suspected and eventually proven [240]. Surgical closure of the tunica should be carried out using absorbable sutures.

4.5.4.5 Penetrating penile trauma

In penetrating penile trauma non-operative management is recommended for small superficial injuries with intact Buck's fascia [310]. 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 [314].

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 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).

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. Skin grafts with thickness of at least 0.4 mm should be used in order to reduce the risk of contraction [314]. Full-thickness skin grafting onto the penile shaft gives less contracture, a better cosmetic appearance and more resistance to trauma during intercourse, when re-established [353]. 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.

4.5.4.6 Penile avulsion injuries and amputation

Acute management involves resuscitation of the patient, 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 [357].

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, but gives higher rates of post-operative urethral stricture and more problems with loss of sensation [358]. 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 suprapubic catheter are placed [359].

If the severed penis cannot be found, or is unsuitable for re-attachment, then the end should be closed as it is done in partial penectomy. Later reconstruction may be employed to lengthen the penis (e.g., suspensory ligament division and V-Y plasty, pseudo-glans formation with split-thickness skin grafting, etc.). A delayed major reconstructive procedure, i.e. phalloplasty (either radial artery or pubic), is sometimes required for injuries which leave a very small or non-functioning penile stump [357].

4.5.4.7 Testicular dislocation

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.

4.5.4.8 Haematocoele

Conservative management is recommended in haematoceles smaller than three times the size of the contralateral testis [360]. In large haematoceles, non-operative management can fail, and delayed surgery (more than 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 [293, 314, 321, 361, 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 [321]. 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.

4.5.4.9 Testicular rupture

It is 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 3.0-absorbable sutures.

4.5.4.10 Penetrating scrotal trauma

Penetrating injuries to the scrotum require surgical exploration with debridement of non-viable tissue. Depending on the extent of the injury, primary reconstruction of the testis and scrotum can usually be performed. In complete disruption of the spermatic cord, re-alignment without vaso-vasostomy may be considered if surgically feasible [363]. Staged secondary microsurgical vaso-vasostomy can be performed after

rehabilitation, although only a few cases have been reported [363]. 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 are lacking.

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 [314]. 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., improvised explosive device blast injury, complex and staged reconstructive surgical procedures are often required [312]. Military testicular salvage rates increased over the last decades due to improvements of medical services (up to 67.6%) [364].

Table 4.5.1: Summary of key points for penile fracture and testicular trauma

Summary of key points:
Penile fracture
The most common causes of penile fracture are sexual intercourse, forced flexion, masturbation and rolling over.
Penile fracture is associated with a sudden cracking or popping sound, pain, immediate detumescence and local swelling.
MRI is superior to all other imaging techniques in diagnosing penile fracture.
Management of penile fracture is surgical intervention with closure of the tunica albuginea.
Testicular Trauma
Blunt testicular injury may occur under intense compression of the testis against the inferior pubic ramus or symphysis, resulting in a rupture of the tunica albuginea.
Testicular rupture is associated with immediate pain, nausea, vomiting, and sometimes fainting.
Scrotal US is the preferred imaging modality for the diagnosis of testicular trauma.
Surgical exploration in patients with testicular trauma ensures preservation of viable tissue when possible.

*4.5.5 **Complications***

The possibility of complications from genital trauma, including psychological effects, erectile dysfunction, urethral stricture, and infertility, is high. In patients with a history of penile fracture post-operative complications were reported in up to 20% of cases, development of plaques or nodules following surgery, post-operative curvature formation and erectile dysfunction occur in 13.9%, 2.8% and 1.9% of patients, respectively [302]. Post-surgical erectile dysfunction is more common in patients > 50 years and those with bilateral corporal involvement [365]. Skin necrosis is rare [305]. The tear size of the tunica albuginea is a parameter which may affect long-term follow-up results [366].

Conservative management of penile fracture increases complications, such as penile abscess, missed urethral disruption, penile curvature, and persistent haematoma requiring delayed surgical intervention [367]. Late complications after conservative management were fibrosis and angulations in 35% and impotence in up to 62% [304, 368].

Post-operative complications were reported in 8% of patients who underwent testicular repair after penetrating trauma [310]. Despite good management and regular follow-up of external genital gunshot wounds, such wounds are fraught with the possibility of complications such as erectile dysfunction, urethral stricture, and infertility. Delayed complications include chronic pain and testicular atrophy. Haematoceles initially treated non-operatively may eventually need delayed surgery if they develop infection or undue pain. Genital injuries are rarely life threatening, but fertility and testosterone production often become the male trauma patient's chief concern once acute issues are resolved [369].

*4.5.6 **Follow-up***

In patients with genital trauma follow-up should focus on diagnosis of and therapy for late complications. Erectile dysfunction, urethral stricture and assessment of fertility are the main concerns [308, 370].

4.5.7 ***Summary of evidence and recommendations for evaluation and management of genital trauma.***

Summary of evidence	LE
A concomitant urethral injury complicates penile fractures and requires specialised management.	3
Ultrasound can determine intra- and/or extra-testicular haematoma, testicular contusion, or rupture with heterogeneous echo pattern parenchyma and loss of contour definition a highly sensitive and specific finding.	3
Surgical treatment of penile fracture ensures the lowest rate of negative long-term sequelae on functional and psychological wellbeing of the patient.	3
In patients with testicular rupture or equivocal imaging, surgical exploration can secure preservation of viable tissue.	3

Recommendations	Strength rating
Exclude urethral injury in the case of penile fracture.	Strong
Perform ultrasound (US) for the diagnosis of testis trauma.	Strong
Treat penile fractures surgically, with closure of tunica albuginea.	Strong
Explore the injured testis in all cases of testicular rupture and in those with inconclusive US findings.	Strong

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6. 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 publicly accessible through the European Association of Urology website: http://uroweb.org/guideline. This guidelines document was developed with the financial support of the European Association of Urology. No external sources of funding and support have been involved. The EAU is a non-profit organisation and funding is limited to administrative assistance and travel and meeting expenses. No honoraria or other reimbursements have been provided.

7. CITATION INFORMATION

The format in which to cite the EAU Guidelines will vary depending on the style guide of the journal in which the citation appears. Accordingly, the number of authors or whether, for instance, to include the publisher, location, or an ISBN number may vary.

The compilation of the complete Guidelines should be referenced as:
EAU Guidelines. Edn. presented at the EAU Annual Congress Paris 2024. ISBN 978-94-92671-23-3.

If a publisher and/or location is required, include:
EAU Guidelines Office, Arnhem, the Netherlands. http://uroweb.org/guidelines/compilations-of-all-guidelines/

References to individual guidelines should be structured in the following way:
Contributors' names. Title of resource. Publication type. ISBN. Publisher and publisher location, year.

EAU Guidelines on Non-Neurogenic Male Lower Urinary Tract Symptoms (LUTS)

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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 have a substantial economic burden. The present Guidelines focuses on offering practical evidence-based guidance on the assessment and treatment of men with various non-neurogenic benign forms of LUTS. The understanding of the lower urinary tract (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). The term BPH is now regarded as inappropriate as it is Benign Prostatic Obstruction (BPO) that is treated if the obstruction is a significant cause of a man's LUTS. It must be emphasised that clinical guidelines present the best evidence available to the experts. However, following guideline recommendations will not necessarily result in the best outcome. Guidelines can never replace clinical expertise when making treatment decisions for individual patients, but rather help to focus decisions - also taking personal values and preferences/individual circumstances of patients into account. Guidelines are not mandates and do not purport to be a legal standard of care.

1.2 Panel composition

The EAU Non-neurogenic Male LUTS Guidelines Panel consists of an international group of experts with urological and clinical epidemiological backgrounds. All experts involved in the production of this document have submitted potential conflict of interest statements which can be viewed on the EAU website Uroweb: http://uroweb.org/guideline/treatment-of-non-neurogenic-male-luts/.

1.3 Available publications

A quick reference document, the Pocket Guidelines, is available in print and on the Uroweb website. 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

*1.4.1 **Publication history***

The Non-neurogenic Male LUTS Guidelines was first published in 2000. Standard procedure for EAU Guidelines includes an annual assessment of newly published literature in the field to guide future updates.

*1.4.2 **Summary of changes***

All chapters of the 2024 Male LUTS Guidelines have been updated, based on the 2022 version of the Guidelines. References have been added throughout the document. Other key changes incorporated in this publication includes:

- A new section 4.2.4 on Symptoms of Lower Urinary Tract Dysfunction Research Network;
- An update in section 4.8 on bladder voiding efficiency;
- A new section 5.2.7.4 regarding α1-blockers + Phosphodiesterase 5 inhibitors including a summary of evidence and recommendations;
- New recommendation in section 5.3.1.1 on open prostatectomy;
- New section in 5.6.2.1 on urodynamic testing for the management of male urinary incontinence;
- A new algorithm for men presenting with urinary incontinence;
- Two new summary of evidence statements in section 5.6.5.3;
- New subchapter on the management of underactive bladder, section 5.7.

2. METHODS

2.1 Introduction

For the 2024 EAU Guidelines on Non-Neurogenic Male LUTS, incl. BPO, new and relevant evidence was identified, collated and appraised through a structured assessment of the literature. A broad and comprehensive literature search, covering all sections of the Non-Neurogenic Male LUTS Guidelines was performed. The search was limited to studies representing high levels of evidence, i.e., systematic reviews (SR) 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 May 1st 2021 and May 1st 2023. A total of 3,608 unique records were identified, retrieved and screened for relevance.

Detailed search strategies for the 2024 guideline are available online:
http://www.uroweb.org/guideline/treatment-of-non-neurogenic-male-luts/supplementary-material.

Recommendation within the Guidelines are developed by the panels to prioritise clinically important care decisions. The strength of each recommendation is determined by the balance between desirable and undesirable consequences of alternative management strategies, the quality of the evidence (including certainty of estimates), and the nature and variability of patient values and preferences. This decision process, which can be reviewed in the strength rating forms which accompany each guideline statement, addresses a number of key elements:

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

Strong recommendations typically indicate a high degree of evidence quality and/or a favourable balance of benefit to harm and patient preference. Weak recommendations typically indicate availability of lower quality evidence, and/or equivocal balance between benefit and harm, and uncertainty or variability of patient preference [2].

Additional methodology information and a list of associations endorsing the EAU Guidelines can be found in the online: https://uroweb.org/eau-guidelines/methodology-policies.

2.2 Review

The Non-Neurogenic Male LUTS Guidelines were peer reviewed prior to publication in 2016. The newly added section on underactive bladder in males was peer reviewed prior to the publication in 2024.

2.3 Patients to whom the guidelines apply

Recommendations apply to men who seek professional help for LUTS in various non-neurogenic and non-malignant conditions such as BPO, detrusor overactivity (DO)/overactive bladder (OAB), urinary incontinence, and/or nocturnal polyuria. Specific context usually requires a more extensive work-up e.g., concomitant neurological diseases, young age, prior LUT disease or surgery, which is not covered in these Guidelines, but may include several tests mentioned in the following sections. EAU Guidelines on Neuro-Urology, Urological Infections, Urolithiasis, or malignant diseases of the LUT have been developed by other EAU Guidelines Panels and are available online: www.uroweb.org/guidelines/.

3. EPIDEMIOLOGY, AETIOLOGY AND PATHOPHYSIOLOGY

Lower urinary tract symptoms can be divided into storage, voiding and post-micturition symptoms [3], and they are prevalent, cause bother and impair QoL [4-7]. An increasing awareness of LUTS and storage symptoms in particular, is warranted to discuss management options that could increase QoL [8]. Lower urinary tract symptoms are strongly associated with ageing [4, 5], associated costs and burden are therefore likely to increase with future demographic changes [5, 9]. Lower urinary tract symptoms are also associated with a number of modifiable risk factors, suggesting potential targets for prevention (e.g., metabolic syndrome) [10]. In addition, men with moderate-to-severe LUTS may have an increased risk of major adverse cardiac events [11].

Most elderly men have at least one LUTS [5]; however, symptoms are often mild or not very bothersome [7, 8, 12]. Lower urinary tract symptoms can progress dynamically: for some individuals LUTS persist and progress over long time periods, and for others they remit [5]. Lower urinary tract symptoms have traditionally been related to bladder outlet obstruction (BOO), most frequently when histological BPH progresses through benign prostatic enlargement (BPE) to BPO [3, 6]. However, increasing numbers of studies have shown that LUTS are often unrelated to the prostate [5, 13]. Bladder dysfunction may also cause LUTS, including

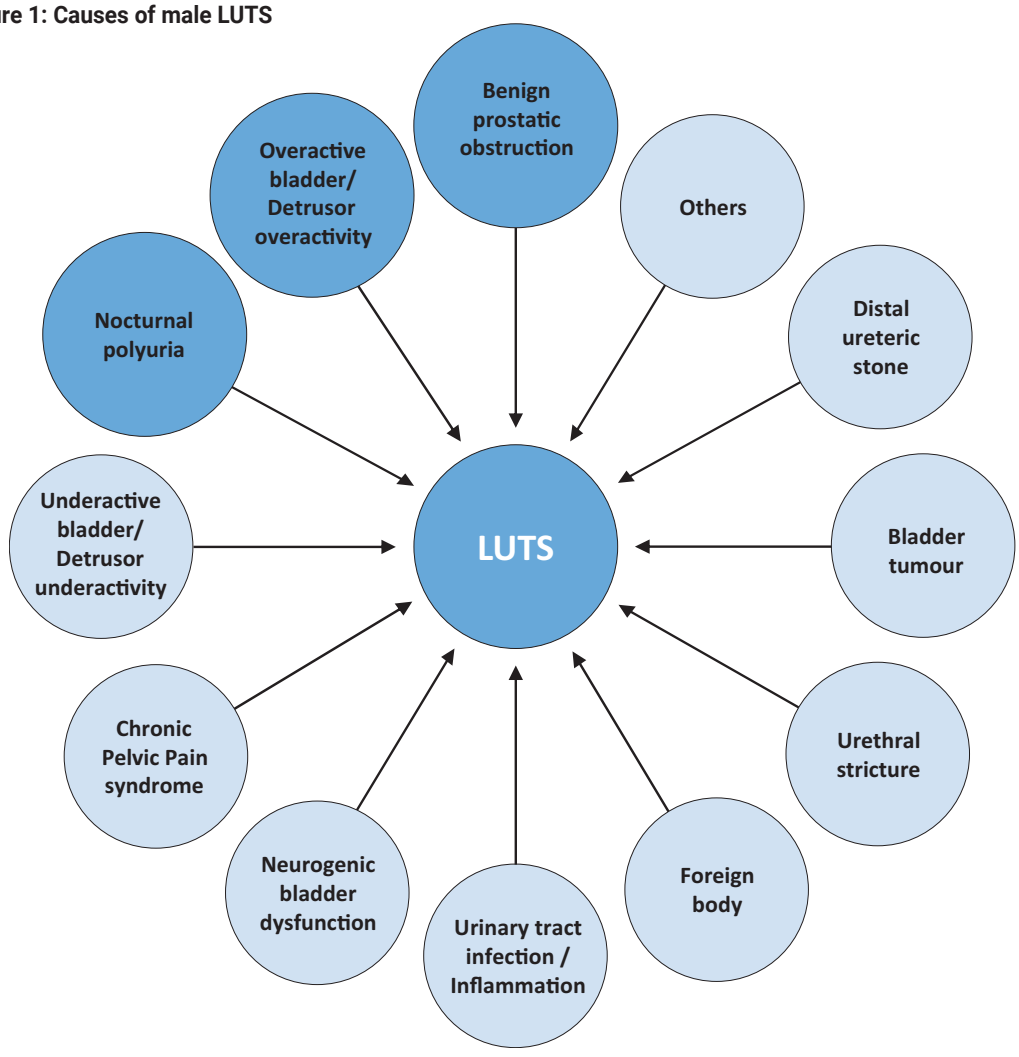
detrusor overactivity/OAB, detrusor underactivity (DU)/underactive bladder (UAB), as well as other structural or functional abnormalities of the urinary tract and its surrounding tissues [13]. Prostatic inflammation also appears to play a role in BPH pathogenesis and progression [14, 15]. In addition, many non-urological conditions also contribute to urinary symptoms, especially nocturia [5].

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 [3].
- 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 [3].
- Bladder outlet obstruction is the generic term for obstruction during voiding and is characterised by increasing detrusor pressure and reduced urine flow rate. It is usually diagnosed by invasive urodynamic or pressure/flow studie [3].
- Benign prostatic obstruction is a form of BOO and may be diagnosed when the cause of outlet obstruction is known to be BPE [3]. In the Guidelines the term BPO or BOO is used as reported by the original studies.
- Benign prostatic hyperplasia is a term used (and reserved) for the typical histological pattern, which defines the disease.
- Detrusor overactivity is a urodynamic observation characterised by involuntary detrusor contractions during the filling phase which may be spontaneous or provoked [3]. Detrusor overactivity is usually associated with OAB syndrome characterised by urinary urgency, with or without urgency urinary incontinence (UUI), usually with increased daytime frequency and nocturia, if there is no proven infection or other obvious pathology [16].
- Detrusor underactivity during voiding is characterised by decreased detrusor voiding pressure leading to a reduced urine flow rate. Detrusor underactivity causes underactive bladder syndrome which is characterised by voiding symptoms similar to those caused by BPO [17].

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 LUTS



4. DIAGNOSTIC EVALUATION

Tests are useful for diagnosis, monitoring, assessing the risk of disease progression, treatment planning, and predicting 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;
- 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 [18-20]. A medical history aims to identify the potential causes and relevant co-morbidities, 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) [21, 22].

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 [18, 20]. Bladder diaries or frequency volume charts (FVC) are particularly beneficial (see section 4.3) [23]. Sexual function should also be assessed, preferably with validated symptom questionnaires such as the International Index of Erectile Function (IIEF) [24].

Summary of evidence	LE
A medical and surgical history is an integral part of a patient's medical evaluation.	4
A medical and surgical history aims to identify the potential causes of LUTS as well as any relevant co-morbidities and to review the patient's current medication and lifestyle habits.	4

Recommendation	Strength rating
Take a complete medical history from men with LUTS.	Strong

4.2 Symptom score questionnaires

All published guidelines for male LUTS recommend using validated symptom score questionnaires [18, 20]. Several questionnaires have been developed which are sensitive to symptom changes and can be used to monitor treatment [25-31]. Symptom scores are helpful in quantifying LUTS and in identifying which type of symptoms are predominant; however, they are not disease-, gender-, or age-specific. A SR 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 [32].

4.2.1 The International Prostate Symptom Score (IPSS)

The IPSS is an eight-item questionnaire, consisting of seven symptom questions and one QoL question [26]. The IPSS score is categorised as 'asymptomatic' (0 points), 'mildly symptomatic' (1-7 points), 'moderately symptomatic' (8-19 points), and 'severely symptomatic' (20-35 points). Limitations include lack of assessment of incontinence, post-micturition symptoms, and bother caused by each separate symptom.

4.2.2 The International Consultation on Incontinence Questionnaire for Male LUTS (ICIQ-MLUTS)

The ICIQ-MLUTS was created from the International Continence Society (ICS) Male questionnaire. It is a widely used and validated patient completed questionnaire including incontinence questions and bother for each symptom [27]. It contains thirteen items, with subscales for nocturia and OAB, and is available in 24 languages. [33]. The ICIQ-MLUTS explore more deeply the subtypes of males LUTS [34].

4.2.3 Danish Prostate Symptom Score (DAN-PSS)

The DAN-PSS [30] is a symptom score used mainly in Denmark and Finland. The DAN-PSS has twelve questions divided into parts A and B with questions on incontinence and measures the bother of each individual LUTS.

4.2.4 The Symptoms of Lower Urinary Tract Dysfunction Research Network (LURN-SI-10)

The LURN-SI-10 correlates strongly with the IPSS but identifies additional important symptomatology including incontinence and bladder pain in men with LUTS [35].

Summary of evidence	LE
Symptom questionnaires are sensitive to symptom changes.	3
Symptom scores can quantify LUTS and identify which types of symptoms are predominant; however, they are not disease-, or age-specific.	3

Recommendation	Strength rating
Use a validated symptom score questionnaire including bother and quality of life assessment during the initial assessment of male LUTS and for re-evaluation during and/or after treatment.	Strong

4.3 Frequency volume charts and/or bladder diaries

The recording of the volume and time of each void by the patient is referred to as an FVC. Inclusion of additional information such as fluid intake, use of pads, activities during recording, or which grades symptom severity and bladder sensation is termed a bladder diary [3]. Parameters that can be derived from the FVC and bladder diary include day-time and night-time voiding frequency, total voided volume, the fraction of urine production during the night (nocturnal polyuria index), and volume of individual voids.

The mean 24-hour urine production is subject to considerable variation. Likewise, circumstantial influence and intra-individual variation cause FVC parameters to fluctuate, though there is comparatively little data [36, 37]. The FVC/bladder diary is particularly relevant in nocturia, where it underpins the categorisation of underlying mechanism(s) [38-40]. The use of FVCs may cause a 'bladder training (BT) effect' and influence the frequency of nocturnal voids [41].

The duration of the FVC/bladder diary needs to be long enough to avoid sampling errors, but short enough to avoid non-compliance [23]. A SR of the available literature recommended FVCs should continue for at least three days [42]. There is no data as to whether the three days should be consecutive or scattered or whether it has to be on weekdays or weekends, as long as it is representative. The ICIQ-Bladder diary (ICIQ-BD) is the only diary that has undergone full validation [43].

Summary of evidence	LE
Frequency volume charts (FVC) and/or bladder diaries provide real-time documentation of urinary function and reduce recall bias.	3
Three- day FVCs provide reliable measurement of urinary symptoms in patients with LUTS similar to seven days and without losing the diagnostic accuracy.	2b

Recommendations	Strength rating
Use a bladder diary to assess male LUTS with a storage component, especially nocturia.	Strong
Tell the patient to complete a bladder diary for at least three days.	Strong

4.4 Physical examination and digital-rectal examination

Physical examination particularly focusing on the suprapubic area, the external genitalia, the perineum, and lower limbs should be performed. Urethral discharge, meatal stenosis, phimosis, and penile cancer must be excluded.

4.4.1 Digital-rectal examination and prostate size evaluation

Digital-rectal examination (DRE) is the simplest way to assess prostate volume, but the correlation to prostate volume is poor. Quality-control procedures for DRE have been described [44]. Transrectal ultrasound (TRUS) is more accurate in determining prostate volume than DRE. There is an underestimation of prostate volume by DRE. The underestimation increases with increasing TRUS volume, particularly where the volume is > 30 mL [45]. A model of visual aids has been developed to help urologists estimate prostate volume more accurately [46]. One study concluded that DRE was sufficient to discriminate between prostate volumes > or < 50 mL [47].

Summary of evidence	LE
Physical examination is an integral part of a patient's medical evaluation.	4
Digital-rectal examination can be used to assess prostate volume and texture; however, the correlation to actual prostate volume is poor.	3

Recommendation	Strength rating
Perform a physical examination including digital rectal examination in the assessment of male LUTS.	Strong

4.5 Urinalysis

Urinalysis (dipstick or microscopy) 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, e.g., Guidelines on urinary tract cancers and urological infections [48-51].

Urinalysis is recommended in most Guidelines in the primary management of patients with LUTS [52, 53]. There is limited evidence, but general expert consensus suggests that the benefits outweigh the costs [54]. The value of urinary dipstick/microscopy for diagnosing UTI in men with LUTS without acute frequency and dysuria has been questioned [55].

Summary of evidence	LE
Urinalysis (dipstick or microscopy) may indicate a UTI, proteinuria, haematuria, or glycosuria requiring further assessment.	3
The benefits of urinalysis outweigh the costs.	4

Recommendation	Strength rating
Use urinalysis (by dipstick or microscopy) in the assessment of male LUTS.	Strong

4.6 Prostate-specific antigen

4.6.1 Prostate-specific antigen and the prediction of prostatic volume

Pooled analysis of RCTs, of men with LUTS and presumed BPO, showed that prostate-specific antigen (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 [56].

A strong association between PSA and prostate volume was found in a large community-based study in the Netherlands [57]. 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 [58, 59].

4.6.2 Prostate-specific angtigen and the probability of PCa

The role of PSA in the diagnosis of PCa is presented by the EAU Guidelines on Prostate Cancer [60]. The potential benefits and harms of using serum PSA testing to diagnose PCa in men with LUTS should be discussed with the patient.

4.6.3 Prostate-specific antigen and the prediction of BPO-related outcomes

Serum PSA is a stronger predictor of prostate growth than prostate volume [61]. In addition, an RCT showed that PSA also predicted the changes in symptoms, QoL/bother, and maximum flowrate (Q_{max}) [62]. In a longitudinal study of men managed conservatively, PSA was a highly significant predictor of clinical progression to urinary retention [63, 64]. In the placebo arms of large double-blind studies, baseline serum PSA predicted the risk of acute urinary retention (AUR) and BPO-related surgery [65, 66]. 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 [67]. Patients with BPO seem to have a higher PSA level and larger prostate volumes. The PPV of PSA for the detection of BPO was recently shown to be 68% [68]. Furthermore, in an epidemiological study, elevated free PSA levels could predict clinical BPE, independent of total PSA levels [69].

Summary of evidence	LE
Prostate-specific antigen (PSA) has a good predictive value for assessing prostate volume and is a strong predictor of prostate growth.	1b
Baseline PSA can predict the risk of AUR and BPO-related surgery.	1b

Recommendations	Strength rating
Measure prostate-specific antigen (PSA) if a diagnosis of prostate cancer will change management.	Strong
Measure PSA if it assists in the treatment and/or decision-making process.	Strong
Counsel patients about PSA testing and the implications of a raised PSA test.	Strong

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 [70]. Even though BPO may be responsible for these complications, there is no conclusive evidence on the mechanism [71].

One study reported that 11% of men with LUTS had renal insufficiency [70]. 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.*, [72] reported that non-neurogenic voiding dysfunction is not a risk factor for elevated creatinine levels. Koch *et al.*, [73] concluded that only those with an elevated creatinine level or reduced eGFR require investigational ultrasound (US) of the kidney and bladder to assess post-void residual.

In the Olmsted County Study, there was a cross-sectional association between signs and symptoms of BPO (though not prostate volume) and chronic kidney disease (CKD) [74]. In 2,741 consecutive patients who presented with LUTS, decreased Q_{max}, a history of hypertension and/or diabetes were associated with CKD [75]. Another study demonstrated a correlation between Q_{max} and eGFR in middle-aged men with moderate-to-severe LUTS [76]. Patients with renal insufficiency are at an increased risk of developing post-operative complications [77].

Summary of evidence	LE
Decreased Q_{max} and a history of hypertension and/or diabetes are associated with CKD in patients who present with LUTS.	3
Patients with renal insufficiency are at an increased risk of developing post-operative complications.	3

Recommendation	Strength rating
Assess renal function if renal impairment is suspected based on history and clinical examination, or in the presence of hydronephrosis, or when considering surgical treatment for male LUTS.	Strong

4.8 Post-void residual urine

Post-void residual (PVR) urine can be assessed by transabdominal ultrasound (US), bladder scan or catheterisation. Post-void residual is not necessarily associated with BOO, since high PVR volumes can be a consequence of obstruction and/or poor detrusor function/DU [78, 79]. Using a PVR threshold of 50 mL, the diagnostic accuracy of PVR measurement has a PPV of 63% and a negative predictive value (NPV) of 52% for the prediction of BOO [80]. A large PVR is not a contraindication to watchful waiting (WW) or medical therapy, although it may indicate a poor response to treatment and especially to WW. In both the MTOPS and ALTESS studies, a high baseline PVR (PVR of ≥ 350 mL) was associated with an increased risk of symptom progression [65, 66].

Monitoring of changes in PVR over time may allow for identification of patients at risk of AUR [81]. This is of importance for the treatment of patients using antimuscarinic medication. In contrast, baseline PVR has little prognostic value for the risk of BPO-related invasive therapy in patients on α1-blockers or WW [82]. However, due to large test-retest variability and lack of outcome studies, no PVR threshold for treatment decision has yet been established; this is a research priority.

Since the role of PVR in males with LUTS has given inconclusive data, bladder voiding efficiency (BVE; [voided volume/total bladder capacity] × 100) has been introduced [83]. This parameter seems to be more reliable than PVR especially in patients with detrusor underactivity [84]. Together with BE, to overcome some limits of PVR, post-void residual urine ratio (PVR-R) was investigated. PVR-R represents the ratio of PVR to bladder volume (BV). This parameter indicates the non-functional bladder storage of urine after micturition and could be better related to the voiding emptying than the PVR per se. it is defined as PVR/total BV) × 100 [85].

Summary of evidence	LE
The diagnostic accuracy of PVR measurement, using a PVR threshold of 50 mL, has a PPV of 63% and a NPV of 52% for the prediction of BOO.	3
Monitoring of changes in PVR over time may allow for identification of patients at risk of AUR.	3

Recommendation	Strength rating
Measure post-void residual in the assessment of male LUTS.	Strong

4.9 Uroflowmetry

Urinary flow rate assessment is a widely used non-invasive urodynamic test. Key parameters are Q_{max}, voided volume, PVR, and flow pattern. Uroflowmetry parameters should preferably be evaluated with voided volume > 150 mL. As Q_{max} is prone to within-subject variation [86, 87], it is useful to repeat uroflowmetry measurements, especially if the voided volume is < 150 mL, or Q_{max} or flow pattern is abnormal.

The diagnostic accuracy of uroflowmetry for detecting BOO varies considerably and is substantially influenced by threshold values. A threshold Q_{max} of 10 mL/s has a specificity of 70%, a PPV of 70% and a sensitivity of 47% for BOO. The specificity using a threshold Q_{max} of 15 mL/s was 38%, the PPV 67% and the sensitivity 82% [88]. 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 [89], DU or an under-filled bladder [90]. Therefore, it is limited as a diagnostic test as it is unable to discriminate between the underlying mechanisms.

Uroflowmetry can be used for monitoring treatment outcomes [91] and correlating symptoms with objective findings [88, 92]. Recently, a deep learning system for sound-based prediction of urinary flow has been proposed, as a simple home-based alternative to uroflowmetry, with acceptable correlation to conventional test [93].

Summary of evidence	LE
The diagnostic accuracy of uroflowmetry for detecting BOO varies considerably and is substantially influenced by threshold values. Specificity can be improved by repeated flow rate testing.	2b

Recommendations	Strength rating
Perform uroflowmetry in the initial assessment of male LUTS.	Weak
Perform uroflowmetry prior to medical or invasive treatment.	Strong

4.10 Imaging

*4.10.1 **Upper urinary tract***

Men with LUTS are not at increased risk for upper tract malignancy or other abnormalities when compared to the overall population [73, 94-96]. Several arguments support the use of renal US in preference to urological computed tomography (UROCT). Ultrasound allows for better characterisation of renal masses, the possibility of investigating the liver and retroperitoneum, and simultaneous evaluation of the bladder, PVR and prostate, together with a lower cost, no radiation dose and less side effects [94]. Ultrasound can be used for the evaluation of men with large PVR, haematuria, or a history of urolithiasis.

Summary of evidence	LE
Men with LUTS are not at increased risk for upper tract malignancy or other abnormalities when compared to the overall population.	3
Ultrasound can be used for the evaluation of men with large PVR, haematuria, or a history of urolithiasis.	4

Recommendation	Strength rating
Perform ultrasound of the upper urinary tract in men with LUTS.	Weak

*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 (suprapubic) US or TRUS [94].

4.10.2.1 Prostate size and shape

Assessment of prostate size is important for the selection of interventional treatment, i.e., open prostatectomy (OP), 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 [96].

Transrectal US is superior to transabdominal volume measurement [97, 98]. The presence of a median lobe may guide treatment choice in patients scheduled for a minimally invasive approach since medial lobe presence can be a contraindication for some minimally invasive treatments (see section 5.3).

Summary of evidence	**LE**
Assessment of prostate size by TRUS or transabdominal US is important for the selection of interventional treatment and prior to treatment with 5-ARIs	3

Recommendations	**Strength rating**
Perform imaging of the prostate when considering medical treatment for male LUTS, if it assists in the choice of the appropriate drug.	Weak
Perform imaging of the prostate when considering surgical treatment.	Strong

*4.10.3 **Voiding cysto-urethrogram***

Voiding cysto-urethrogram (VCUG), on its own, 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 diseases and can be combined with urodynamics in the form of video-urodynamics. Retrograde urethrography may additionally be useful for the evaluation of suspected urethral strictures.

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. The evaluation of a prostatic middle lobe with urethrocystoscopy should be performed when considering interventional treatments for which the presence of middle lobe may affect the treatment offered e.g., Urolift.

A prospective study evaluated 122 patients with LUTS using uroflowmetry and urethrocystoscopy [99]. The pre-operative Q_{max} was normal in 25% of 60 patients who had no bladder trabeculation, 21% of 73 patients with mild trabeculation and 12% of 40 patients with marked trabeculation on cystoscopy. All 21 patients who presented with diverticula had a reduced Q_{max}.

Another study 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 [100]. The largest study published on this issue examined the relation of urethroscopic findings to urodynamic studies in 492 elderly men with LUTS [101]. 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 [101].

Summary of evidence	**LE**
Patients with a history of microscopic or gross haematuria, urethral stricture, or bladder cancer, who present with LUTS, should undergo urethrocystoscopy during diagnostic evaluation.	3
No study clearly identified a strong association between the urethrocystoscopic and urodynamic findings.	3

Recommendation	**Strength rating**
Perform urethrocystoscopy in men with LUTS prior to minimally invasive/surgical therapies if the findings may change treatment.	Weak

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 (UDS) is to explore the functional mechanisms of LUTS, to identify risk factors for adverse outcomes and to provide information for shared decision-making. Most terms and conditions (e.g., DO, low compliance, BOO/BPO, DU) are defined by urodynamic investigation.

4.12.1 ***Diagnosing bladder outlet obstruction***

Pressure flow studies are used to diagnose and define the severity of BOO, which is characterised by increased detrusor pressure and decreased urinary flow rate during voiding. Bladder outflow obstruction/ BPO has to be differentiated from DU, which exhibits decreased detrusor pressure during voiding in combination with decreased urinary flow rate [3]. Bladder outlet obstruction is calculated according to the equation $p_{det}Q_{max} – 2Q_{max}$ (BOO>40 = obstructed; BOO 20-40 = equivocal; and BOO<20 = unobstructed) [102], and to assess the contractility of the bladder, BCI is calculated according to the equation $P_{det}Q_{max}+5Q_{max}$ [103] (BCI>150 = strong contractility, 100-150 = normal contractility, and < 100 weak contractility) [83].

Urodynamic testing may also identify DO. Studies have described an association between BOO and DO [104, 105]. In men with LUTS attributed to BPO, DO was present in 61% and independently associated with BOO grade and ageing [104].

The prevalence of DU in men with LUTS is 11-40% [106, 107]. Detrusor contractility does not appear to decline in long-term BOO and surgical relief of BOO does not improve contractility [108, 109]. The UPSTREAM trial investigated whether urodynamics would reduce surgery without increasing urinary symptoms. UPSTREAM was a non-inferiority, RCT in men with bothersome LUTS, in whom surgery was an option, in 26 hospitals in England. In the UDS arm, 153/408 patients (38%) received surgery compared with 138/384 (36%) in the routine care (RC) arm. A total of 428 adverse events were recorded, with related events similar in both arms and eleven unrelated deaths. The UDS group was non-inferior to the RC group for IPSS, and UDS did not significantly reduce surgical rates. The authors concluded that routine use of UDS in the evaluation of uncomplicated LUTS has a limited role and should be used selectively [110]. However, in a prospective cohort study of urodynamically assessed patients prior to surgery, patients with DU alone with Bladder Contractility Index (BCI) [BCI] < 100 and BOO index [BOOI] < 40 had significantly worse outcome with regard to post-operative maximum flow rate at twelve month than those DU and BOO with BCI < 100 and BOOI ≥ 40) as well as patients with BOO alone with and BCI ≥ 100 and BOOI ≥ 40) [111]. Nevertheless, if urodynamic investigation is performed, a rigorous quality control is mandatory [112, 113].

Exploratory findings from the UPSTREAM Trial have characterised the basic diagnostic and urodynamic parameters to identify men who will benefit more from de-obstructive surgery [114]. The Investigators reported that surgery was more beneficial in those men with higher symptom scores (IPSS>16), age<74yr, poor urine flow (Q_{max} < 10ml/s), bladder outlet obstruction index > 47.6 and bladder contractility index > 123.

Due to the invasive nature of the test, a urodynamic investigation is generally only offered if conservative and medical treatment have failed. The Guidelines Panel attempted to identify specific indications for UDS based on age, findings from other diagnostic tests and previous treatments. The Panel allocated a different degree of obligation for UDS in men > 80 years and men < 50 years, which reflects the lack of evidence. In addition, there was no consensus whether UDS 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 UDS 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 [115].

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. There is only low-level evidence for the addition of imaging to UDS.

Summary of evidence	**LE**
Pressure-flow studies is not a test for routine use prior to prostate surgery for all patients.	3

Recommendations	Strength rating
Perform urodynamics (UDS) only in individual patients for specific indications prior to invasive treatment or when further evaluation of the underlying pathophysiology of LUTS is warranted.	Weak
Perform UDS in men who have had previous unsuccessful (invasive) treatment for LUTS prior to further invasive treatment.	Weak
Perform UDS in men considering invasive treatment who cannot void > 150 mL.	Weak
Perform UDS when considering surgery in men with bothersome predominantly voiding LUTS and Q_{max} > 10 mL/s.	Weak
Perform UDS when considering invasive therapy in men with bothersome, predominantly voiding LUTS with a post-void residual > 300 mL.	Weak
Perform UDS when considering invasive treatment in men with bothersome, predominantly voiding LUTS aged > 80 years.	Weak
Perform UDS when considering invasive treatment in men with bothersome, predominantly voiding LUTS aged < 50 years.	Weak

4.13 Non-invasive tests in diagnosing bladder outlet obstruction in men with LUTS

4.13.1 Prostatic configuration/intravesical prostatic protrusion

Prostatic configuration can be evaluated with TRUS, using the concept of the presumed circle area ratio (PCAR) [116]. The PCAR evaluates how closely the transverse US image of the prostate approaches a circular shape. The ratio tends toward one as the prostate becomes more circular. The sensitivity of PCAR was 77% for diagnosing BPO when PCAR was > 0.8, with 75% specificity [116].

Ultrasound measurement of intravesical prostatic protrusion (IPP) assesses the distance between the tip of the prostate median lobe and bladder neck in the midsagittal plane, using a suprapubically positioned US scanner, with a bladder volume of 150-250 mL; grade I protrusion is 0-4.9 mm, grade II is 5-10 mm and grade III is > 10 mm.

Intravesical prostatic protrusion correlates well with BOO, with a PPV of 94% and a NPV of 79% [117]. A SR examined the role of IPP in UDS determined BOO [118]. At cut-off > 10mm the sensitivity was found 0.71 and the specificity 0.77. Intravesical prostatic protrusion may also correlate with prostate volume, DO, bladder compliance, detrusor pressure at maximum urinary flow, BOO index and PVR, and negatively correlates with Q_{max} [119]. Furthermore, IPP also appears to successfully predict the outcome of a trial without catheter after AUR [120, 121]. Evidence from the above-mentioned SR, showed that at an IPP cut-off of > 10mm, the sensitivity and specificity to predict unsuccessful voiding trial without catheter (TWOC) was 0.51 and 0.79 respectively [118]. However, no information with regards to intra- or inter-observer variability and learning curve is yet available. Therefore, whilst IPP may be a feasible option to infer BPO in men with LUTS, the role of IPP as a non-invasive alternative to PFS in the assessment of male LUTS remains 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 [122].

A correlation between BWT and UDS 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 [123]. Detrusor wall thickness at the anterior bladder wall with a bladder filling > 250 mL (threshold value for BOO > 2 mm) has a PPV of 94% and a specificity of 95%, achieving 89% agreement with PFS [73]. 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 [124]. A meta-analysis reported that DWT has high accuracy in diagnosing BOO with sensitivity 71% and specificity 88% [125].

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 UDS, BOO or DO. However, the study did not use a specific bladder filling volume for measuring BWT [126]. Disadvantages of the method include the lack of standardisation, and lack of evidence to indicate which measurement (BWT/DWT) is preferable [127]. 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 [128, 129]. Severe LUTS and a high UEBW (> 35 g) are risk factors for prostate/BPO surgery in men on α-blockers [130].

4.13.3 Non-invasive pressure-flow testing

The penile cuff test (PCT), in which flow is interrupted to estimate isovolumetric bladder pressure, shows promising data, with good test repeatability [131] and interobserver agreement [132]. A nomogram has also been derived [133] whilst a method in which flow is not interrupted is also under investigation [134]. A SR and meta-analysis assessed the performance of PCT to recognise BOO, reported sensitivity 0.85, specificity 0.78, PPV 0.74 and NPV 0.87 [135]. However, there was marked heterogeneity among the included studies in the definition of obstruction.

The data generated with the external condom method [136] correlates with invasive PFS in a high proportion of patients [137]. Resistive index [138] and prostatic urethral angle [139] 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

A SR including 42 studies investigated the diagnostic performance of non-invasive tests in diagnosing BOO in men with LUTS compared with UDS/PFS [140]. The majority of the included studies were prospective cohorts, focusing on BOO and not specifically on BPO, and the diagnostic accuracy of the following non-invasive tests were assessed: penile cuff test; uroflowmetry; DWT/BWT; bladder weight; external condom catheter method; IPP; Doppler US; prostate volume/height; and near-infrared spectroscopy. Overall, although the majority of studies have a low risk of bias, data regarding the diagnostic accuracy of these non-invasive tests is limited by the heterogeneity of the studies in terms of the threshold values used to define BOO, the different urodynamic definitions of BOO used across different studies and the small number of studies for each test. It was found that specificity, sensitivity, PPV and NPV of the non-invasive tests were highly variable. Therefore, even though several tests have shown promising results regarding non-invasive diagnosis of BOO, invasive urodynamics remains the modality of choice.

The diagnostic performance of non-invasive tests could be theoretically improved when two or more tests are combined along with clinical parameters, however the evidence is still limited. Investigators have proposed a model and a clinical nomogram that uses BWT, prostate volume and PVR ratio to predict BOO with reported accuracy 0.82 [141].

Summary of evidence	**LE**
Data regarding the diagnostic accuracy of non-invasive tests is limited by the heterogeneity of the studies as well as the small number of studies for each test.	1a
Specificity, sensitivity, PPV and NPV of the non-invasive tests were highly variable.	1a

Recommendation	**Strength rating**
Do not offer non-invasive tests as an alternative to urodynamics/pressure-flow studies for diagnosing bladder outflow obstruction in men.	Strong

4.14 Novel assessment

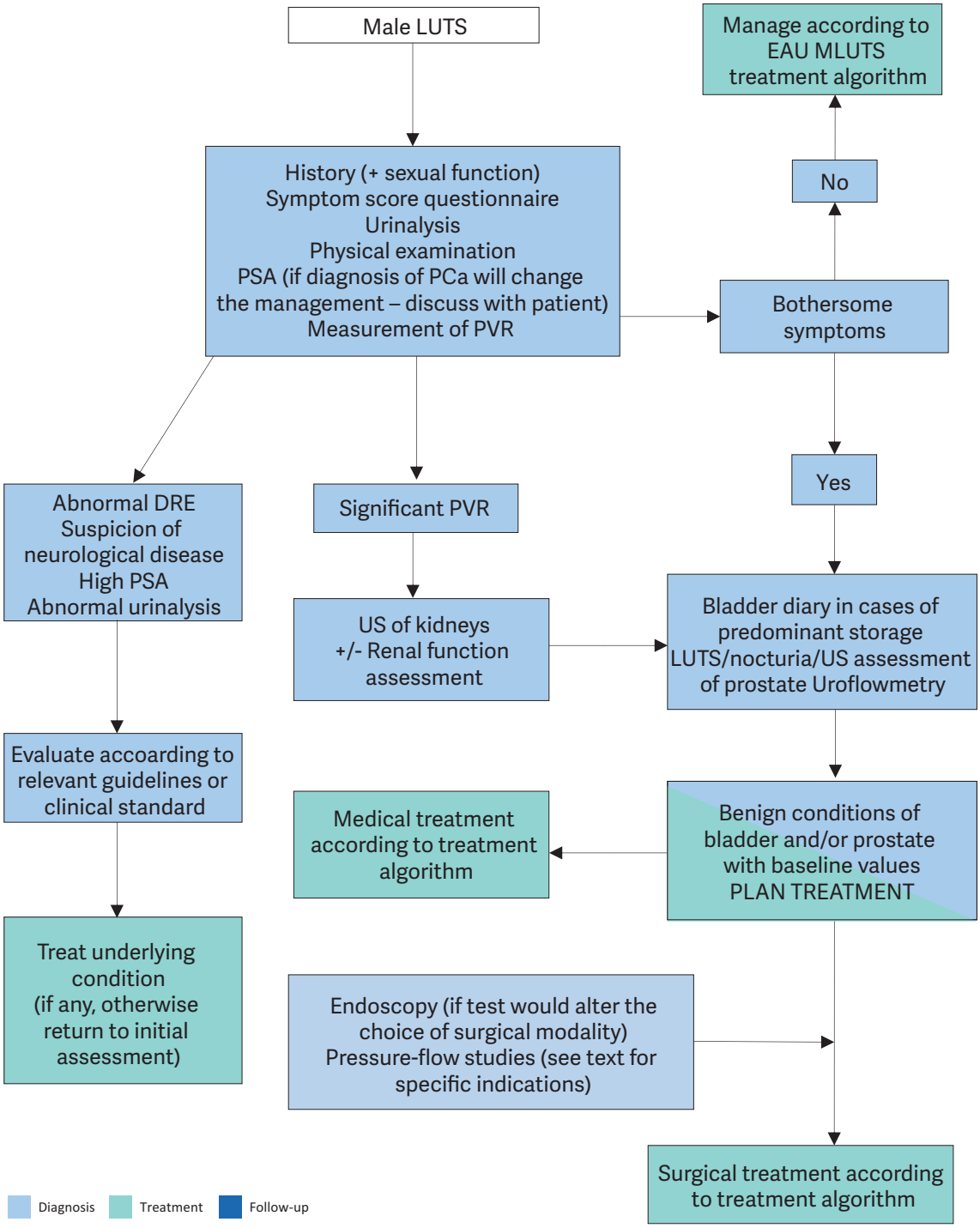
4.14.1 Visual prostate symptom score

A novel visual prostate symptom score (VPSS) has been prospectively tested vs. the IPPS and correlated positively with the IPSS score [142, 143]. This visual score can be used as an option in men with limited literacy.

4.14.2 Micro-RNA

The use of miR-221 has been shown to have the potential to be used as a biomarker and novel target in the early diagnosis and therapy of BPH [144].

Figure 2: Assessment algorithm of LUTS in men aged 40 years or older
Readers are strongly recommended to read the full text that highlights the current position of each test in detail.



DRE = digital-rectal examination; FVC = frequency volume chart; LUTS = lower urinary tract symptoms; PCa = prostate cancer; PSA = prostate specific antigen; PVR = post-void residual; US = ultrasound.

5. DISEASE MANAGEMENT

5.1 Conservative treatment

5.1.1 Watchful waiting

Many men with LUTS are not troubled enough by their symptoms to need drug treatment or surgical intervention. All men with LUTS should be formally assessed prior to any allocation of treatment in order to establish symptom severity and to differentiate between men with uncomplicated (the majority) and complicated LUTS. Watchful waiting is a viable option for many men with non-bothersome LUTS as few will progress to AUR and complications (e.g. renal insufficiency or stones) [145, 146], whilst others can remain stable for years [147]. In one study, approximately 85% of men with mild LUTS were stable on WW at one year [148].

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 [149, 150]. Increasing symptom bother and PVR volumes are the strongest predictors of WW 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 [147, 148, 151, 152] such as:
    - 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);
    - 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;
    - use of relaxed and double-voiding techniques;
    - urethral milking to prevent post-micturition dribble;
    - 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 OAB symptoms;
    - bladder retraining that encourages men to hold on when they have urgency to increase their bladder capacity and the time between voids;
    - 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);
    - providing necessary assistance when there is impairment of dexterity, mobility, or mental state;
    - treatment of constipation.

Evidence exists that self-management as part of WW reduces both symptoms and progression [151, 152]. Men randomised to three self-care 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 [151]. A SR and meta-analysis found reasonable certainty in estimates that self-management intervention significantly reduced symptom severity in terms of IPSS at six months compared with usual care [153]. The reduction in IPSS score with self-management was similar to that achieved with drug therapy at six to twelve weeks. Self-management had a smaller, additional benefit at six weeks when added to drug therapy [153].

5.1.3 Practical considerations

The components of self-care management have not been individually studied. The above components of lifestyle advice have been derived from formal consensus methodology [154]. Further research in this area is required.

Summary of evidence	LE
Watchful waiting is usually a safe alternative for men who are less bothered by urinary difficulty or who wish to delay treatment. The treatment failure rate over a period of five years was 21%; 79% of patients were clinically stable.	1b
An additional study reported 81% of patients were clinically stable on WW after a mean follow-up of seventeen months.	2
Men randomised to three self-management sessions in addition to standard care had better symptom improvement and QoL than men treated with standard care alone at up to a year. Self-care management as part of WW reduces both symptoms and progression.	1b
Self-management achieved a clinically meaningful reduction in symptom severity at six months compared to usual care. There was also a small but significant additional benefit of adding self-management to drug therapy.	1b

Recommendations	Strength rating
Offer men with mild/moderate symptoms, minimally bothered by their symptoms, watchful waiting.	Strong
Offer men with LUTS lifestyle advice and self-care information prior to, or concurrent with, treatment.	Strong

5.2 Pharmacological treatment

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 [155]. However, α1-blockers have little effect on urodynamically determined bladder outlet resistance [156], and treatment-associated improvement of LUTS correlates poorly with obstruction [157]. Thus, other mechanisms of action may also be relevant.

Alpha 1-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. Alpha 1-adrenoceptors in blood vessels, other non-prostatic smooth muscle cells, and the central nervous system may mediate adverse events.

Currently available α1-blockers are: alfuzosin hydrochloride (alfuzosin); doxazosin mesylate (doxazosin); silodosin; tamsulosin hydrochloride (tamsulosin); terazosin hydrochloride (terazosin); and naftopidil. Alpha 1-blockers exist in different formulations. Although different formulations result in different pharmacokinetic and tolerability profiles, the overall difference in clinical efficacy between the difference formulations seems negligible.

Efficacy: Indirect comparisons and limited direct comparisons between α1-blockers demonstrate that all α1-blockers have a similar efficacy in appropriate doses [158]. Clinical effects take a few weeks to develop fully, but significant efficacy over placebo can occur within hours to days [157].

Controlled studies show that α1-blockers typically reduce IPSS by approximately 30-40% and increase Q_{max} by approximately 20-25%. However, substantial improvements also occurred in the corresponding placebo arms [63, 159]. In open-label studies, an IPSS improvement of up to 50% and Q_{max} increase of up to 40% were documented [63, 159]. A SR and meta-analysis suggested that Q_{max} variation underestimates the real effect of α1-blockers on BPO, as small improvements in Q_{max} correspond to relevant improvements in BOO index in PFS [160].

Alpha 1-blockers can reduce both storage and voiding LUTS. Prostate size does not affect α1-blocker efficacy in studies with follow-up periods of less than one year, but α1-blockers do seem to be more efficacious in patients with smaller prostates (< 40 mL) in longer-term studies [65, 161-164]. The efficacy of α1-blockers is similar across age groups [159]. A pooled analysis of phase III and IV trials of silodosin 8 mg demonstrated that improvements in total, storage, voiding, and QoL IPSS scores were similar for the severe and not severe LUTS cohorts [165]. In addition, α1-blockers neither reduce prostate size nor prevent AUR in long-term studies [162-164]; however, evidence suggests that the use of α1-blockers (alfuzosin, tamsulosin and silodosin) improve resolution of AUR [166, 167]. Nonetheless, 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 with alfuzosin and tamsulosin [168]. Patients with cardiovascular co-morbidity and/or vaso-active co-medication may be susceptible to α1-blocker-induced vasodilatation [169]. In contrast, the frequency of hypotension with the α1A-selective blocker silodosin is comparable with placebo [170]. In a large retrospective cohort analysis of men aged > 66 years treated with α1-blockers the risks of falling (odds ratio [OR] 1.14) and of sustaining a fracture (OR 1.16) was increased, most likely as a result of induced hypotension [171]. In terms of cardiovascular risk, a large population-based study reported an increased risk of cardiac failure with long-term α-blocker use (HR 1.22), which was higher for non-selective α-blockers [172]. Whilst there has been concern about a possible risk of dementia with long-term use of α1-blockers, a large Finnish nationwide case-control study of 24,602 cases and 98,397 controls did not find evidence of a significant association [173].

An adverse ocular event termed intra-operative floppy iris syndrome (IFIS) was reported in 2005, affecting cataract surgery [174]. A meta-analysis on IFIS after alfuzosin, doxazosin, tamsulosin or terazosin exposure showed an increased risk for all α1-blockers [175]. However, the OR 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 SR concluded that α1-blockers do not adversely affect libido, or erectile function (ED), but can cause abnormal ejaculation (OR: 7.53) [176]. 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 meta-analysis ejaculatory dysfunction (EjD) was significantly more common with α1-blockers than with placebo (OR: 5.88). In particular, EjD was significantly more commonly related with tamsulosin or silodosin (OR: 8.57 and 32.5) than placebo, while both doxazosin and terazosin (OR: 0.80 and 1.78) were associated with a low risk of EjD [177]. 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 usually considered the first-line drug treatment for 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 occurrence of urinary retention or need for surgery. Ophthalmologists should be informed about α1-blocker use prior to cataract surgery. Elderly patients treated with non-selective α1-blockers should be informed about the risk of orthostatic hypotension. Sexually active patients treated with selective α1-blockers should be counselled about the risk of EjD.

Summary of evidence	**LE**
Alpha 1-blockers are effective in reducing urinary symptoms (IPSS) and increasing the peak urinary flow rate (Q_{max}) compared with placebo.	1a
Alfuzosin, terazosin and doxazosin showed a statistically significant increased risk of developing vascular-related events compared with placebo.	1a
Alfuzosin, doxazosin, tamsulosin and terazosin exposure has been associated with an increased risk of IFIS.	1a
Ejaculatory dysfunction is significantly more common with α1-blockers than with placebo, particularly with more selective α1-blockers such as tamsulosin and silodosin.	1a

Recommendation	**Strength rating**
Offer α1-blockers to men with moderate-to-severe LUTS.	Strong

*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 [178], which has two isoforms:

- 5α-reductase type 1: predominant expression and activity in the skin and liver.
- 5α-reductase type 2: predominant expression and activity in the prostate.

Two 5-ARIs are available for clinical use: dutasteride and finasteride. Finasteride inhibits only 5α-reductase type 2, whereas dutasteride inhibits both 5α-reductase types (dual 5-ARI). The 5-ARIs induce apoptosis of prostate epithelial cells [179] leading to prostate size reduction of about 18-28% and a decrease in circulating PSA levels of about 50% after six to twelve months of treatment [180]. Mean prostate volume and PSA reduction 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 treatment of at least six 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 [65, 163, 164, 181-187]. An indirect comparison and one direct comparative trial (twelve months duration) indicated that dutasteride and finasteride are equally effective in the treatment of LUTS [180, 188]. Symptom reduction depends on initial prostate size.

Finasteride may not be more efficacious than placebo in patients with prostates < 40 mL [189]. 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 [190, 191]. 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 the α1-blocker tamsulosin [163, 187, 192]. The greater the baseline prostate volume (or serum PSA level), the faster and more pronounced the symptomatic benefit of dutasteride as compared to tamsulosin.

5α-reductase inhibitors, but not α1-blockers, reduce the long-term (> 1 year) risk of AUR or need for surgery [65, 185, 193]. In the PLESS study, finasteride reduced the relative risk of AUR by 57% and need for surgery by 55% (absolute risk reduction 4% and 7%, respectively) at four years, compared with placebo [185]. In the MTOPS study, finasteride reduced the relative risk of AUR by 68% and need for surgery by 64% (absolute risk reduction 2% and 3%, respectively), also at four years [65]. A pooled analysis of three RCTs with two-year follow-up data, reported that treatment with finasteride decreased the relative risk of AUR by 57%, and surgical intervention by 34% (absolute risk reduction 2% for both) in patients with moderately symptomatic LUTS [194]. Dutasteride has also demonstrated efficacy in reducing the risks for AUR and BPO-related surgery. Open-label trials have demonstrated relevant changes in urodynamic parameters [195, 196]. Furthermore, finasteride might reduce blood loss during transurethral prostate surgery, probably due to its effects on prostatic vascularisation, although evidence for a clinically significant effect is mixed [197-199].

Tolerability and safety: The most common adverse events are reduced libido, erectile dysfunction (ED) and less frequently, ejaculation disorders such as retrograde ejaculation, ejaculation failure, or decreased semen volume [65, 164, 180, 200]. Gynaecomastia (with breast or nipple tenderness) develops in 1-2% of patients. Two studies have suggested that treatment with 5-ARIs is associated with a higher incidence of high-grade cancers although no causal relationship has been proven [201, 202]. There is a long-standing debate regarding potential cardiovascular side effects of 5-ARIs, in particular dutasteride [203]. Population-based studies in Taiwan and Ontario did not find an association between the use of 5-ARIs and increased cardiovascular side effects [203, 204]. In a British-Taiwanese population-based cohort study, the risk of type II diabetes was higher in men with 5-ARIs than in men receiving tamsulosin but did not differ between dutasteride and finasteride [205]. A large Swedish cohort study showed an increased risk of depression with both finasteride (HR 1.61) and dutasteride (HR 1.68), but no long-term association with dementia or suicide risk [206].

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). They can prevent the risk of AUR and need for surgery. Due to the slow onset of action, they are not suitable for short-term use. Their effect on PSA needs to be considered in relation to PCa screening.

Summary of evidence	**LE**
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.	1b
5α-reductase inhibitors can prevent disease progression with regard to AUR and the need for surgery. Due to 5-ARIs slow onset of action, they are suitable only for long-term treatment (years).	1a
The most relevant adverse effects of 5-ARIs are related to sexual function, and include reduced libido, ED and less frequently, ejaculation disorders such as retrograde ejaculation, ejaculation failure, or decreased semen volume as well as breast enlargement and breast tenderness.	1b

Recommendations	Strength rating
Use 5α-reductase inhibitors (5-ARIs) in men who have moderate-to-severe LUTS and an increased risk of disease progression (e.g., prostate volume > 40 mL).	Strong
Counsel patients about the slow onset of action of 5-ARIs.	Strong

*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 and epithelial cells of the salivary glands. Five muscarinic receptor subtypes (M1-M5) have been described, of which M2 and M3 are predominant in the detrusor. The M2 subtype is more numerous, but the M3 subtype is functionally more important in bladder contractions [207, 208]. Antimuscarinic effects might also be induced or modulated through other cell types, such as the bladder urothelium or by the central nervous system [209, 210].

The following muscarinic receptor antagonists are licensed for treating OAB/storage symptoms: darifenacin hydrobromide (darifenacin); fesoterodine fumarate (fesoterodine); oxybutynin hydrochloride (oxybutynin); propiverine hydrochloride (propiverine); solifenacin succinate (solifenacin); tolterodine tartrate (tolterodine); and trospium chloride. Transdermal preparations of oxybutynin have been formulated and evaluated in clinical trials [211, 212].

Efficacy: Antimuscarinics were mainly tested in females in the past, as it was believed that LUTS in men were caused by the prostate, so should be treated with prostate-specific drugs. However, there is no scientific data for this assumption [213]. A sub-analysis of an open-label trial of OAB patients showed that age, but not gender had an impact on urgency, frequency, or urgency incontinence [214]. In a pooled analysis, which included a sub-analysis of male patients, fesoterodine 8 mg was superior to tolterodine extended release (ER) 4 mg for the improvement of severe urgency episodes/24 hours and the OAB-q Symptom Bother score at week twelve, the urinary retention rate was around 2% [215].

The efficacy of antimuscarinics as single agents in men with OAB in the absence of BOO have been tested [216-221]. Most trials lasted only twelve weeks. Four *post hoc* analyses of large RCTs on the treatment of OAB in women and men without presumed BOO were performed focusing only on the men [213, 217, 222]. Tolterodine can significantly reduce urgency incontinence, daytime or 24-hour frequency and urgency-related voiding whilst improving patient perception of treatment benefit [223]. 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 UUI episodes. In open-label trials with tolterodine, daytime frequency, nocturia, UUI, and IPSS were significantly reduced compared with baseline values after twelve to 25 weeks [218, 221]. The TIMES RCT reported that tolterodine ER monotherapy significantly improved UUI episodes per 24 hours compared to placebo, at week twelve. Tolterodine ER did not significantly improve urgency, IPSS total or QoL score compared with placebo [220].

A further analysis showed that men with PSA levels of < 1.3 ng/mL (smaller prostates) might benefit more from antimuscarinics [224]. Two other studies found a positive effect of antimuscarinics in patients with OAB and concomitant BPO [221, 225]. In a small RCT propiverine improved frequency and urgency episodes [225].

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) [218]. 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 twelve 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) [226]. 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 [213].

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 symptom scores and PVR is advised. Men should be advised to discontinue medication if worsening voiding LUTS or urinary stream is noted after initiation of therapy.

Summary of evidence	LE
Antimuscarinic monotherapy can significantly improve urgency, UUI, and increased daytime frequency.	2
Antimuscarinic monotherapy can be associated with increased PVR after therapy, but acute retention is a rare event in men with a PVR volume of < 150 mL at baseline.	2

Recommendations	Strength rating
Use muscarinic receptor antagonists in men with moderate-to-severe LUTS who mainly have bladder storage symptoms.	Strong
Do not use antimuscarinic overactive bladder medications in men with a post-void residual volume > 150 mL.	Weak

*5.2.4 **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. The mode of action of beta-3 agonists is not fully elucidated [227].

Efficacy: Mirabegron 50 mg is the first clinically available beta-3 agonist with approval for use in adults with OAB. Mirabegron has undergone extensive evaluation in RCTs conducted in Europe, Australia, North America, and Japan [228-232]. Mirabegron demonstrated significant efficacy in treating the symptoms of OAB, including micturition frequency, urgency and UUI and also patient perception of treatment benefit. These studies had a predominantly female study population. A meta-analysis of eight RCTs including 10,248 patients (27% male) found that mirabegron treatment resulted in reduced frequency, urgency and UUI rates, as well as an improved voided volume with a statistically significant improvement of nocturia compared with both placebo and tolterodine [233].

Mirabegron has been evaluated in male patients with OAB in the context of LUTS either associated or not associated with BPO confirmed by urodynamics [234]. Mirabegron 25 mg daily led to increased satisfaction and improved QoL, but symptoms assessed by validated questionnaires (IPSS and OAB-SS), only improved in non-obstructed patients. Mirabegron as an add-on therapy has been studied in OAB patients with incontinence despite antimuscarinic therapy [235], again in a predominantly female study population. An Asian study with a higher proportion of male subjects (approximately one third) reported superiority over placebo in reducing frequency of micturition but did not report the results separately for the genders [236].

In a study of more than 1,000 patients of whom approximately 30% were male, combination therapy of mirabegron 25/50 mg and solifenacin 5/10 mg was associated with statistically significant improvements in patient outcomes and health related QoL vs. solifenacin 5 mg and placebo; however, they did not separate out the effects in men and women [237]. In another study, in which 28% patients were male, mirabegron significantly improved patient reported perception of their condition and QoL whether or not patients were incontinent [238]. A phase IV study, with a small proportion of male subjects, reported addition of mirabegron in people with persisting urgency despite solifenacin in a Japanese population [239].

An RCT has suggested Mirabegron might lead to improvement of urinary symptoms and sexual function in patients suffering from BPO and concurrent erectile dysfunction [240]. The study showed a significant improvement in the IIEF-15 total score and IPSS score in patients treated with Mirabegron + Doxazosin [240]. Nevertheless, further multicentre RCTs with large numbers of patients are required to consolidate these data.

Tolerability and safety: The most common treatment-related adverse events in the mirabegron groups were hypertension, UTI, headache and nasopharyngitis [228-231]. Mirabegron is contraindicated in patients with severe uncontrolled hypertension (systolic blood pressure ≥ 180 mmHg or diastolic blood pressure ≥ 110 mmHg, or both). Blood pressure should be measured before starting treatment and monitored regularly during treatment. A combination of thirteen clinical studies including 13,396 patients, 25% of whom were male, showed that OAB treatments (anticholinergics or mirabegron) were not associated with an increased risk of hypertension or cardiovascular events compared to placebo [241]. 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 [228]. 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 BCI [242]. The overall change in PVR with mirabegron is small [242].

A small prospective study (mainly focused on males) has shown that mirabegron 25 mg is safe in patients aged 80 years or more with multiple co-morbidities [243]. A pooled analysis of three trials, each of twelve weeks and a one-year trial showed, in patients aged > 65 years, a more favourable tolerability profile for mirabegron than antimuscarinics [244]. The PILLAR phase IV study also showed that in a large population of 888 patients ≥ 65 years (approx. 30% of males), mirabegron 50 mg was safe and effective [245]. In an eighteen-week study of 3,527 patients (23% male), the incidence of adverse events was higher in the combination (solifenacin 5 mg plus mirabegron 25 mg) group (40%) than the mirabegron 25 mg alone group (32%). Events recorded as urinary retention were low (< 1%) but were reported slightly more frequently in the combined group when compared with the monotherapy and placebo groups. The PVR volume was slightly increased in the combined group compared with solifenacin 5 mg, and the mirabegron monotherapy and placebo groups. Combined therapy with solifenacin 5 mg plus mirabegron 25 mg and solifenacin 5 mg plus mirabegron 50 mg provided improvements in efficacy generally consistent with an additive effect [246].

In a retrospective analysis of persistence and adherence in 21,996 patients, of whom 30% were male, the median time to discontinuation was significantly longer for mirabegron (169 days) compared to tolterodine (56 days) and other antimuscarinics (30-78 days). There was no statistical difference between men and women [247].

The phase III EMPOWUR trial comparing vibegron to placebo and tolterodine showed once daily 75 mg vibegron provided statistically significant reductions in micturitions, urgency episodes and UUI [248]. Treatment was well tolerated with a favourable safety profile. However, the majority of the study population (85%) were female and vibegron is not yet licenced in Europe.

Practical considerations: Long-term studies on the efficacy and safety of mirabegron in men of any age with LUTS are not yet available. Available studies on mirabegron in combination with antimuscarinics in OAB patients had a predominantly female study population, while further trials are still pending.

Summary of evidence	**LE**
Mirabegron improves storage LUTS, including urinary frequency, urgency and UUI.	2
Patients prescribed mirabegron remained on treatment longer than those prescribed antimuscarinics.	3

Recommendation	**Strength rating**
Use beta-3 agonists in men with moderate-to-severe LUTS who mainly have bladder storage symptoms.	Weak

*5.2.5 **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 PDE5Is might also alter reflex pathways in the spinal cord and neurotransmission in the urethra, prostate, or bladder [249]. Moreover, chronic treatment with PDE5Is seems to increase blood perfusion and oxygenation in the LUT [250]. Phosphodiesterase 5 inhibitors could also reduce chronic inflammation in the prostate and bladder [251]. The exact mechanism of PDE5Is on LUTS remains unclear.

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: Randomised controlled trials have demonstrated that PDE5Is reduce IPSS, storage and voiding LUTS, and improve QoL. However, Q_{max} did not significantly differ from placebo in most trials [252]. A Cochrane review included a total of sixteen RCTs that examined the effects of PDE5Is compared to placebo and other standard of care drugs (α1-blockers and 5-ARIs) in men with LUTS [253]. In the updated meta-analysis, PDE5Is led to a small reduction (mean difference (MD) 1.89 lower; 95% CI: 2.27 lower to 1.50 lower; n = 4293) in IPSS compared to placebo [253]. There was no difference between PDE5Is and α1-blockers in IPSS [254]. Most evidence was limited to short-term treatment up to twelve weeks. In other meta-analyses, PDE5Is were also found to improve IPSS and IIEF score, but not always Q_{max} [255, 256]. A meta-regression suggested that younger men with low body mass index and more severe LUTS benefit the most from treatment with PDE5Is [255].

In a post hoc analysis of data pooled from four blinded trials of tadalafil 5 mg vs. placebo once daily, a minimum improvement of 25% in IPSS score was found in 60% in the tadalafil and in 44% in the placebo group [257]. The maximum trial duration was 52 weeks [258]. 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 [259]. In a *post hoc* analysis of pooled data from four RCTs, tadalafil was shown to also be effective in men with cardiovascular risk factors/co-morbidities, except for patients receiving more than one antihypertensive medication. Among sexually active men > 45 years, tadalafil improved both LUTS/BPH and ED [259].

An integrated data analyses from four placebo controlled clinical studies showed that total IPSS improvement was largely attributed to direct (92.5%) vs. indirect (7.5%) treatment effects via IIEF-EF improvement [260]. Another analysis showed a small but significant increase in Q_{max} without any effect on PVR [261]. An integrated analysis of RCTs showed that tadalafil was not superior to placebo for IPSS improvement at twelve weeks in men ≥ 75 years (with varied effect size between studies) but was for men < 75 years [262]. An open label urodynamic study of 71 patients showed significant improvements in both voiding and storage symptoms, confirmed by improvements in BOO index (61.3 to 47.1), and resolution of DO in fifteen (38%) of 38 patients. Flow rate improved from 7.1 to 9.1 mL/s and mean IPSS from 18.2 to 13.4 [263].

A multicentre, double blind, placebo controlled RCT compared once daily tadalafil 20 mg vs. placebo during twelve weeks in men with LUTS with or without BOO. Urodynamic measures including detrusor pressure at maximum urinary flow rate, Q_{max}, maximum detrusor pressure, BOO or bladder capacity remained largely unchanged during the study with no statistically significant or clinically adverse event differences between tadalafil and placebo [264].

A study has shown that in patients with OAB and LUT obstruction unresponsive to previous treatment, the simultaneous administration of solifenacin, tadalafil, and dutasteride could be an effective and safe choice [265].

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 [255].

Tadalafil is contraindicated in patients using nitrates or guanylate cyclase stimulators, such as riociguat, and in men with cardiac disease for whom sexual activity is inadvisable [266]. Tadalafil is also contraindicated in patients with myocardial infarction within the last 90 days, - patients with unstable angina or angina occurring during sexual intercourse, - patients with New York Heart Association Class 2 or greater heart failure in the last six months, - patients with uncontrolled arrhythmias, hypotension (< 90/50 mm Hg), or uncontrolled hypertension, - patients with a stroke within the last six months or if anterior ischaemic optic neuropathy with sudden loss of vision is known or was reported after previous use of PDE5Is [266]. Detailed information regarding tolerability/safety of all available PDE5Is for the treatment of erectile dysfunction in men treated with α-blockers for LUTS are provided by the EAU Guidelines on Sexual and Reproductive Health [267].

Practical considerations: To date, only tadalafil 5 mg once daily has been officially licensed for the treatment of male LUTS with or without ED. Long-term experience with tadalafil in men with LUTS is limited to one trial with a one-year follow-up [258]; limiting conclusions about efficacy or tolerability greater than one year. There is limited information on reduction of prostate size and no data on disease progression.

Summary of evidence	**LE**
Phosphodiesterase 5 inhibitors significantly improve IPSS and IIEF score, but not Qmax.	1a

Recommendation	**Strength rating**
Use phosphodiesterase type 5 inhibitors in men with moderate-to-severe LUTS with or without erectile dysfunction.	Strong

*5.2.6 **Plant extracts – phytotherapy***

Potential mechanism of action: Herbal drug preparations are made of roots, seeds, pollen, bark, or fruits. There are single plant preparations (mono-preparations) and preparations combining two or more plants in one pill (combination preparations) [268].

Possible relevant compounds include phytosterols, ß-sitosterol, fatty acids, and lectins [268]. 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 acetylcholine receptors, dihydropyridine receptors and vanilloid receptors; and neutralise free radicals [263, 268, 269]. The *in vivo* effects of these compounds are uncertain, 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 [270]. In addition, batches from the same producer may contain different concentrations of active ingredients [271]. A review of recent extraction techniques and their impact on the composition/biological activity of available *Serenoa repens* based products showed that results from different clinical trials must be compared strictly according to the same validated extraction technique and/or content of active compounds [272], as the pharmacokinetic properties of the different preparations can vary significantly.

Heterogeneity and a limited regulatory framework characterise the current status of phytotherapeutic agents. The European Medicines Agency (EMA) has developed the Committee on Herbal Medicinal Products (HMPC). European Union (EU) herbal monographs contain the HMPC's scientific opinion on safety and efficacy data about herbal substances and their preparations intended for medicinal use. The HMPC evaluates all available information, including non-clinical and clinical data, whilst also documenting long-standing use and experience in the EU. European Union monographs are divided into two sections: a) Well established use (marketing authorisation): when an active ingredient of a medicine has been used for more than ten years and its efficacy and safety have been well established (including a review of the relevant literature); and b) Traditional use (simplified registration): for herbal medicinal products which do not fulfil the requirements for a marketing authorisation, but there is sufficient safety data and plausible efficacy on the basis of long-standing use and experience.

The HPMC periodically invites all interested parties to submit any scientific data that the Committee should consider during their periodic review of the monographs. Table 1 lists the available EU monographs for herbal medicinal products and the current calls for update.

Table 1: European Union monographs for herbal medicinal products [273]

Herbal substance	HMPC evaluation	Therapeutic Indication by HMPC	Date of monograph
Serenoa repens, fructus (saw palmetto, fruit) Extraction solvent: hexane [274]	Well established use	Symptomatic treatment of BPH	14/01/2016 Addendum 1/9/21**
Serenoa repens, fructus (saw palmetto, fruit) Extraction solvent: ethanol [274]	Traditional use	LUTS related to BPH*	14/01/2016 Addendum 1/9/21**
Cucurbita pepo L, semen (pumpkin seed) Preparation as defined in the monograph [275]	Traditional use	LUTS related to BPH or related to an OAB*	25/03/2013 Call ended 30/4/21
Prunus africana (Hook f.) Kalkm., cortex (pygeum africanum bark) Preparation as defined in the monograph [276]	Traditional use	LUTS related to BPH*	01/09/2017 No call for update
Urtica dioica L., Urtica urens L., their hybrids or their mixtures, radix Preparation as defined in the monograph [277]	Traditional use	LUTS related to BPH*	05/11/2012 Call ended 30/6/21
Epilobium angustifolium L. and/or *Epilobium parviflorum Schreb., herba (Willow herb)* Preparation as defined in the monograph [278]	Traditional use	LUTS related to BPH*	13/01/2016 No call for update

** After serious conditions have been excluded by a medical doctor.*
*** Addendum concluded that no revision was needed.*

Panel interpretation: Only hexane extracted *Serenoa repens* (HESr) has been recommended for well-established use by the HMPC. Based on this a detailed scoping search covering the timeframe between the search cut-off date of the EU monograph and May 2021 was conducted for HESr.

A large meta-analysis of 30 RCTs with 5,222 men and follow-up ranging from four to 60 weeks, demonstrated no benefit of treatment with *S. repens* in comparison to placebo for the relief of LUTS [279]. It was concluded that *S. repens* was not superior to placebo, finasteride, or tamsulosin with regard to IPSS improvement, Q_{max}, or prostate size reduction; however, the similar improvement in IPSS or Q_{max} compared with finasteride or tamsulosin could be interpreted as treatment equivalence. Importantly, in the meta-analysis all different brands of *S. repens* were included regardless or not of the presence of HESr as the main ingredient in the extract.

Another SR focused on data from twelve RCTs on the efficacy and safety of HESr [280]. It was concluded that HESr was superior to placebo in terms of improvement of nocturia and Q_{max} in patients with enlarged prostates. Improvement in LUTS was similar to tamsulosin and short-term use of finasteride. An updated SR analysed fifteen RCTs and also included twelve observational studies. It confirmed the results of the previous SR on the efficacy of HESr [281]. Compared with placebo, HESr was associated with 0.64 (95% CI: 0.98 - 0.31) fewer voids/night and an additional mean increase in Q_{max} of 2.75 mL/s (95% CI: 0.57 - 4.93), both were significant. When compared with α-blockers, HESr showed similar improvements in IPSS (WMD 0.57; 95% CI: 0.27 - 1.42) and a comparable increase in Q_{max} when compared to tamsulosin (WMD 0.02; 95% CI: 0.71 - 0.66). Efficacy assessed using IPSS was similar after six months of treatment between HESr and 5-ARIs. Analysis of all available published data for HESr showed a mean significant improvement in IPSS from baseline of 5.73 points (95% CI: 6.91 - 4.54) [281].

A network meta-analysis tried to compare the clinical efficacy of *S. repens* (HESr and non-HESr) against placebo and α1-blockers in men with LUTS. Interestingly, only two RCTs on HESr were included in the analysis. It was found that *S. repens* achieved no clinically meaningful improvement against placebo or α1-blockers in short-term follow-up. However, *S. repens* showed a clinical benefit after a prolonged period of treatment, and HESr demonstrated a greater improvement than non-HESr in terms of IPSS [282].

With respect to safety and tolerability data from the SRs showed that HESr had a favourable safety profile with gastrointestinal disorders being the most frequent adverse effects (mean incidence 3.8%) while HESr had very limited impact on sexual function.

A cross-sectional study compared the combination of HESr with silodosin, to silodosin monotherapy in patients treated for at least twelve months (mean duration 13.5 months) [283]. It was reported that 69.9% of the combination therapy patients achieved the predefined clinically meaningful improvement (improvement more than three points in baseline IPSS) compared to 30.1% of patients treated only with silodosin. In addition, a greater than 25% improvement in IPSS was found in 68.8% and 31.2% of the patients in the combination and the monotherapy groups, respectively. These data suggest that combination of a α1-blocker with HESr may result in greater clinically meaningful improvements in LUTS compared to α1-blocker monotherapy [283].

Practical considerations: Available RCTs do not use the same endpoints (e.g., IPSS). More studies on the use of HESr in combination with other pharmacotherapeutic agents for male LUTS are pending. There is a need to define the subpopulation of patients who will benefit most from therapy with HESr.

Summary of evidence	**LE**
Hexane extracted *Serenoa repens* improves Q_{max} and results in fewer voids/night (0.64 [95% CI: 0.98 to 0.31]) compared to placebo.	2
Hexane extracted *Serenoa repens* has a very limited negative impact on sexual function.	2

Recommendations	**Strength rating**
Offer hexane extracted *Serenoa repens* to men with LUTS who want to avoid any potential adverse events especially related to sexual function.	Weak
Inform the patient that the magnitude of efficacy may be modest.	Strong

*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. Initial studies with follow-up periods of six to twelve months demonstrated that the α1-blocker was superior to finasteride in symptom reduction, whereas combination therapy of both agents was not superior to α1-blocker monotherapy [182, 183, 284]. 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 [65].

Long-term data (four years) from the MTOPS and CombAT studies showed that combination treatment is superior to monotherapy for symptoms and Q_{max}, and superior to α1-blocker alone in reducing the risk of AUR or need for surgery [65, 163, 164].

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 [164]. Thus, the differences in MTOPS may reflect different inclusion and exclusion criteria and baseline patient characteristics.

Discontinuation of the α1-blocker after six to nine months of combination therapy was investigated in an RCT and an open-label multicentre trial [285, 286]. The first trial evaluated the combination of tamsulosin with dutasteride and the impact of tamsulosin discontinuation after six months [285], 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 [286]. Lower urinary tract symptom improvement after combination therapy was sustained at three months (IPSS difference 1.24) and nine months (IPSS difference 0.4). The limitations of the studies include short duration and short follow-up period after discontinuation.

In both the MTOPS and CombAT studies, combination therapy was superior to monotherapy in preventing clinical progression as defined by an IPSS increase of at least four points, AUR, UTI, incontinence, or an increase in creatinine > 50%. The MTOPS study found that the risk of long-term clinical progression (primarily due to increasing IPSS) was reduced by 66% with combined therapy vs. placebo and to a greater extent than with either finasteride or doxazosin monotherapy (34% and 39%, respectively) [65]. In addition, finasteride (alone or in combination), but not doxazosin alone, significantly reduced both the risks of AUR and the need for BPO-related surgery over the four-year study. In the CombAT study, combination therapy reduced the relative risks of AUR by 68%, BPO-related surgery by 71%, and symptom deterioration by 41% compared with tamsulosin, after four years [287]. To prevent one case of urinary retention and/or surgical treatment, thirteen patients need to be treated for four years with dutasteride and tamsulosin combination therapy compared to tamsulosin monotherapy while the absolute risk reduction (risk difference) was 7.7%.

The CONDUCT study compared efficacy and safety of a fixed-dose combination of dutasteride and tamsulosin to a WW approach with the potential initiation of tamsulosin (step-up approach) in a two-year RCT with a total of 742 patients. In both arms detailed lifestyle advice was given. This fixed-dose combination resulted in a rapid and sustained improvement in men with moderate LUTS at risk of disease progression, the difference in IPSS at 24 months was 5.4 in the active arm and 3.6 in the placebo arm [288]. Furthermore, tamsulosin plus dutasteride significantly reduced the relative risk of clinical progression (mainly characterised as a worsening in symptoms) by 43.1% when compared with WW, with an absolute risk reduction of 11.3% (number needed to treat [NNT] = 9).

The influence of baseline variables on changes in IPSS after combination therapy with dutasteride plus tamsulosin or either monotherapy was tested based on the four-year results of the CombAT study. Combination therapy provided consistent improvement of LUTS over tamsulosin across all analysed baseline variables at 48 months [289].

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 section 5.2.5 [290].

Tolerability and safety: Adverse events for both drug classes have been reported with combination treatment [65, 163, 164]. 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. The MTOPS study demonstrated that the incidence of treatment related adverse events is higher during the first year of combined treatment between doxazosin and finasteride [291]. A meta-analysis measuring the impact of medical treatments for LUTS/BPH on ejaculatory function, reported that combination therapy with α1-blockers and 5-ARIs resulted in a three-fold increased risk of EjD compared with each monotherapy [177].

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 who are at risk of disease progression (higher prostate volume, higher PSA concentration, advanced age, higher PVR, lower Q_{max}, etc.). Combination therapy should only be used when long-term treatment (more than twelve months) is intended, and patients should be informed of this. Discontinuation of the α1-blocker after six months might be considered in men with moderate LUTS.

Summary of evidence	**LE**
Long-term data (four years) from the MTOPS and CombAT studies showed that combination treatment is superior to monotherapy for symptoms and Qmax, and superior to α1-blocker alone in reducing the risk of AUR or need for surgery.	1b
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.	1b
The CombAT study found that 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.	1b
Adverse events of both drug classes are seen with combined treatment using α1-blockers and 5-ARIs.	1b

Recommendation	**Strength rating**
Offer combination treatment with an α1-blocker and a 5α-reductase inhibitor to men with moderate-to-severe LUTS and an increased risk of disease progression (e.g. prostate volume > 40 mL).	Strong

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 to date.

Efficacy: Several RCTs and prospective studies investigated combination therapy, lasting four to twelve weeks, either as an initial treatment in men with OAB and presumed BPO or as a sequential treatment for storage symptoms persisting while on an α1-blocker [212, 223, 287, 292-296]. Combination treatment has marginal efficacy in reducing urgency, UUI, voiding frequency, nocturia, or IPSS compared with α1-blockers or placebo alone, and improves QoL [223, 296]. A SR and meta-analysis of RCTs (six studies of treatment-naïve patients, and five studies of men with persistent storage LUTS despite prior treatment with α-blockers) concluded that the addition of antimuscarinics to α-blockers marginally reduced number of micturition episodes per day (standard mean difference -0.19) but did not have a significant impact on number of urgency episodes, and had a higher side effect profile [297]. Similar findings were also reported in a Cochrane review of RCTs of men with LUTS secondary to BPO, with a small improvement in IPSS (mean difference 2.04) and QoL (mean difference 0.71) with combination therapy compared to α-blocker monotherapy, although overall certainty of evidence was deemed moderate to very low [298].

Symptom improvement is higher regardless of PSA concentration with combination therapy, whereas tolterodine alone improved symptoms mainly in men with a serum PSA of < 1.3 ng/mL [224].

In a meta-analysis of sixteen studies with 3,548 patients with BPH/OAB, initial combination treatment of an α1-blocker with anticholinergic medication showed no difference in total IPSS and Q_{max} between the two groups [299].

Effectiveness of therapy is evident primarily in those men with moderate-to-severe storage LUTS [300]. Long term use of combination therapy has been reported in patients receiving treatment for up to one year, showing symptomatic response is maintained, with a low incidence of AUR [301]. 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 QoL compared with placebo and α1-blocker monotherapy [302].

Combined behavioural and drug therapy yielded greater improvements in OAB symptoms than drug therapy alone, but not behavioural therapy alone in a RCT evaluating the effectiveness of combined behavioural strategies and drug therapy for OAB symptoms in men [303].

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 dry mouth. Some side-effects (e.g. dry mouth 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 up to one year of treatment [220, 304, 305]. Antimuscarinics do not cause evident deterioration in Q_{max} used in conjunction with an α1-blocker in men with OAB symptoms [296, 306].

An RCT investigated safety in terms of maximum detrusor pressure and Qmax for solifenacin (6 mg or 9 mg) with tamsulosin in men with LUTS and BOO compared with placebo [307]. The combination therapy was non-inferior to placebo for the primary urodynamic variables; Q_{max} was increased vs. placebo [307].

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.

Summary of evidence	LE
Combination treatment with α1-blockers and antimuscarinics is effective for improving LUTS-related QoL impairment.	2
Combination treatment with α1-blockers and antimuscarinics is more effective for reducing urgency, UUI, voiding frequency, nocturia, or IPSS compared with α1-blockers or placebo alone.	2
Adverse events of both drug classes are seen with combined treatment using α1-blockers and antimuscarinics.	1
There is a low risk of AUR using α1-blockers and antimuscarinics in men known to have a PVR volume of < 150 mL.	2

Recommendations	Strength rating
Use combination treatment of a 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.	Weak
Do not prescribe combination treatment in men with a post-void residual volume > 150 mL.	Weak

5.2.7.3 α1-blockers + Beta-3 agonist

Mechanism of action: Combination therapy consists of an α1-blocker (Section 5.2.1) together with a beta-3-agonist (Section 5.2.4) as an add-on therapy in males receiving α1-blockers with persisting OAB symptoms.

Efficacy: The MATCH study explored the effect of the addition of mirabegron 50 mg to tamsulosin 0.2 mg compared to tamsulosin plus placebo in 544 patients [308]. A statistically significant difference of 0.52 voids per day was seen in favour of mirabegron. Total IPSS score also improved but was not significant between the groups. Another RCT evaluated add-on therapy with mirabegron for OAB symptoms persisting after treatment with tamsulosin 0.2 mg daily in men with BPO [309]. Combination therapy was associated with greater improvements in OAB symptom score, in urinary urgency and daytime frequency as well as the storage sub-score of IPSS and QoL index compared to monotherapy with tamsulosin [310].

The PLUS phase IV trial [309] compared mirabegron and placebo in a population of males treated with a standard dose of tamsulosin 0.4 mg. After a four-week run-in period of treatment with tamsulosin 0.4 mg alone, 715 patients were randomised between placebo and mirabegron 25 mg, upgraded to 50 mg after one month. While mean number of micturition's were significantly reduced in the experimental arm, the effect size was deemed as low (mean adjusted difference of 0.39 voids per day). Similar results were seen for mean voided volume and urgency episodes, but total IPSS, IPSS sub-scores and OAB-q symptom score were not significantly different between the groups.

An RCT comparing the efficacy of mirabegron 50 mg or fesoterodine 4 mg add-on therapy to silodosin in LUTS patients with persisting OAB symptoms reported that at three months, fesoterodine add-on therapy showed a significantly greater improvement than mirabegron add-on therapy in OAB symptom score and urgency score and IPSS-QoL score [237]. Fesoterodine was also superior in alleviating DO.

Tolerability and safety: In the MATCH study main adverse events were in line with previous trials, and cardiovascular events were uncommon in the studied populations [308]. The PLUS phase IV trial also reported adverse events similar to those seen in previous trials (hypertension, headache and nasopharyngitis being the

most frequent) [309]. There were six episodes of retention recorded (1.7%) and overall, no clinically significant specific change was seen in Q_{max} and PVR. An open-label, randomised, 2-arm, 2-sequence study reported that the addition of mirabegron or tamsulosin to patients under tamsulosin or mirabegron mono therapy did not cause clinically relevant changes in cardiovascular safety or safety profiles [311].
Solifenacin and mirabegron were also compared in another RCT that has shown comparable efficacy but a better safety profile for mirabegron [312].

Practical consideration: Add-on therapy with mirabegron in patients with remaining symptoms under α1-blocker therapy has been evaluated only in short-term clinical trials. The short-term benefit remains uncertain with a low effect size in urinary frequency compared to placebo, and more studies with longer follow-up are required

Summary of evidence	LE
Combination treatment with α1-blockers and mirabegron results in a slight decrease of number of voids and urgency episodes per day compared with α1-blockers alone.	1b
Adverse events of both drug classes are seen with combined treatment using α1-blockers and mirabegron.	1b

Recommendations	Strength rating
Use combination treatment of a α1-blocker with mirabegron in patients with persistent storage LUTS after treatment with α1-blocker monotherapy.	Weak

5.2.7.4 α1-blockers + Phosphodiesterase 5 inhibitors

Mechanism of action: Combination treatment consists of an α1-blocker together with a phosphodiesterase 5 inhibitor (Section 5.2.5) with the intent to achieve better improvements in LUTS.

Efficacy: A meta-analysis of five RCTs (two studies with tadalafil 20 mg daily, 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 [255]. Both a SR and Cochrane review found similar findings, and a network meta-analysis of 55 RCTs (excluding 5-ARIs) found that the combination of PDE5Is and α-blockers had greater IPSS improvement than monotherapy and any other combination therapy [253, 313, 314]. These results have been confirmed by prospective studies which have shown an improvement in the IPSS QoL, IIEF-5 score and Q_{max} in patients taking PDE5Is and α-blockers [252, 315].

Tolerability and safety: No serious AEs have been reported in the association of PDE5-Is and α-blockers. In RCT comparing α-blockers alone with combined therapy, AEs occur with similar incidence across the two treatments arms suggesting that the addition of PDE5Is to α-blockers is well tolerated [316].

Practical consideration: The combination of α-blockers and PDE5Is versus α-blockers monotherapy leads to greater improvements in LUTS, QoL, erectile function and Q_{max} without increase in AEs.
Data from meta-analyses suggest how younger men with low body mass index and more severe LUTS may be the population that benefits most from this association [255]. However, further studies with large populations and longer follow-up are needed to confirm these findings.

Summary of evidence	LE
Combination of PDE5Is and alpha blockers improves IPSS, but magnitude of effect of clinical significance is low.	1a

Recommendations	Strength rating
Use combination treatment of a α1-blockers + Phosphodiesterase 5 inhibitors in patients with bothersome LUTS, particularly in patients willing to improve their erectile function.	Weak
Inform the patients that the magnitude of the effect is modest.	Weak

Note: All patients should be counselled about pharmacological treatment related adverse events in order to select the most appropriate treatment for each individual patient

5.3 Surgical treatment of benign prostatic obstruction

Surgical treatment is one of the cornerstones of LUTS/BPO management. Based on its ubiquitous availability, as well as its efficacy, monopolar TURP (M-TURP) has long been considered as the reference technique for the surgical management of LUTS/BPO. However, in recent years various techniques have been developed with the aim of providing a safe and effective alternative to M-TURP. Previously, the surgical section of the Guidelines was based on technology rather than surgical approach. As the clinical reality is primarily reflected by surgical approach and not necessarily by a specific technology, the chapter on surgical management has been restructured. It is now divided into the following five sections:

1. Resection;
2. Enucleation;
3. Vaporisation;
4. Alternative ablative techniques; and
5. Non-ablative techniques.

In addition, most of the studies are restricted by prostate size, which is also reflected in the present Guidelines. Notably, only a small fraction of RCTs are performed in patients with a prostate > 80 mL; therefore, high-level evidence for larger prostates are limited.

Based on Panel consensus, timeframes defining short-, mid- and long-term follow-up of patients submitted to surgical treatments are twelve, 36, and over 36 months, respectively. The durability of a technique is reflected by the re-operation rate during follow-up, the failure to wean patients off medication as well as the initiation of novel LUTS medication after surgery. However, for the majority of techniques only the re-operation rate is reported, and clinicians should inform patients that long-term surgical RCTs are often lacking. Some patients value sexual function and perceived higher safety over maximum efficacy and it is not therefore surprising that some patients consciously choose an alternative ablative or non-ablative technique despite the knowledge that it might not be their definitive treatment. In contrast, many urologists are critical about these procedures due to their inferior relief of BOO.

Recommendations on new devices or interventions will only be included in the Guidelines once supported by a minimum level of evidence. To clarify this the Panel have published their position on certainty of evidence (CoE) [317]. In summary, a device or technology is only included once supported by RCTs looking at both efficacy and safety, with adequate follow-up, and secondary studies to confirm the reproducibility and generalisability of the first pivotal studies [317]. Otherwise, there is a danger that a single pivotal study can be overexploited by device manufacturers. Studies that are needed include proof of concept, RCTs on efficacy and safety, as well as cohort studies with a broad range of inclusion and exclusion criteria to confirm both reproducibility and generalisability of the benefits and harms [317]. The panel assesses the quality of all RCTs and if they do not meet the standard required the intervention will continue to have no recommendation i.e., an RCT does not guarantee inclusion in the Guidelines.

In addition, the Guidelines continues to include techniques under investigation. These are devices or technologies that have shown promising results in initial studies; however, they do not meet the aforementioned criteria yet to provide a CoE which allows the Panel to regard these devices or technologies as recommended alternatives. To account for evolving evidence, recommendations for some techniques under investigation have been made; however, these techniques remain under investigation until further studies provide the recommended CoE.

*5.3.1 **Resection of the prostate***

5.3.1.1 Monopolar and bipolar transurethral resection of the prostate

Mechanism of action: Transurethral resection of the prostate is either performed in a M-TURP or bipolar TURP (B-TURP) fashion. Transurethral resection of the prostate removes tissue from the transition zone of the gland in various degrees resulting in a volume and PSA reduction of 25 -58%. 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) using normal saline for irrigation thereby eliminating TUR-syndrome [318, 319].

Efficacy: In a meta-analysis of twenty RCTs with a maximum follow-up of five years, M-TURP resulted in a substantial mean Q_{max} improvement (+162%), a significant reduction in IPSS (-70%), QoL score (-69%), and PVR (-77%) [320]. Monopolar-TURP delivers durable outcomes as shown by studies with a follow-up of eight to 22 years [321]. One study with a mean follow-up of thirteen years reported a significant and sustained decrease in most symptoms and improvement in urodynamic parameters. Failures were associated with DUA rather than re-growth of BPH [109]. A second prostatic operation, usually re-TURP, has been reported at a constant annual

rate of approximately 1-2%. A SR analysing 29 RCTs found a retreatment rate of 2.6% after a mean follow-up of sixteen months [322]. Data from an Austrian nationwide study of two cohorts totalling 41,059 men submitted to M-TURP showed that the overall retreatment rates (re-TURP, urethrotomy and bladder neck incision) remained unchanged during the last decade (0.9%, 3.7%, 9.5% and 12.7% at three months, one year, five years, and eight years, respectively), and that the respective incidence of re-TURP was 0.8%, 2.4%, 6.1% and 8.3%, respectively [323, 324].

Bipolar TURP is the most widely investigated alternative to M-TURP. Pooled results from 59 RCTs have been reported to date [325]. Early pooled results as well as at twelve months, concluded that no clinically relevant differences exist in short-term efficacy (IPSS, QoL score and Q_{max}) [325, 326]. Subsequent meta-analyses supported these conclusions though trial quality was generally poor [320, 327-330]. The largest meta-analysis published to date, confirmed that B-TURP compared to M-TURP results in little to no difference in urological symptoms and bother (IPSS and QoL score) at twelve months [325]. Data from RCTs with mid- to long-term follow-up (up to 60 months) showed no differences in efficacy parameters [331-339]. A meta-analysis of RCTs comparing B-TURP vs. M-TURP, reported similar efficacy at 36 months in terms of IPSS, and Q_{max} [340].

A meta-analysis was conducted to evaluate the quasi-bipolar transurethral resection in saline (TURis), Olympus Medical system vs. M-TURP. Ten unique RCTs (1,870 patients) were included, and it was concluded that TURis was of equivalent efficacy to M-TURP [341].

Tolerability and safety: Peri-operative mortality and morbidity of M-TURP have decreased over time, but morbidity remains considerable (0.1% and 11.1%, respectively) [342]. Data from an Austrian nationwide study of two cohorts totalling 41,059 men submitted to M-TURP showed a 20% reduction in mortality rate over time, to 0.1% at 30 days and 0.5% at 90 days [323, 324].

The risk of TUR-syndrome decreased to < 1.1% [322, 343]. Data from 10,654 M-TURPs reported bleeding requiring transfusion in 2.9% [342]. Short- to mid-term complications reported in an analysis of RCTs using M-TURP as a comparator were: 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%) [320]. Long-term complications of M-TURP comprise urinary incontinence (UI), urinary retention and UTIs, bladder neck contracture (BNC), urethral stricture, retrograde ejaculation and ED [322].

Early pooled results concluded that no differences exist in short-term urethral stricture/BNC rates, but B-TURP is preferable to M-TURP 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) [326]. Subsequent meta-analyses supported these conclusions [320, 327-330, 340]; however, trial quality was relatively poor and limited follow-up might cause under-reporting of late complications, such as urethral stricture/BNC [326]. The largest meta-analysis published to date, concluded that B-TURP compared to M-TURP reduced TUR-syndrome and blood transfusion events by twenty and 28 fewer events per 1,000 participants, respectively [325]. The study also concluded that B-TURP may carry a similar risk of UI and may result in similar rates of re-TURP in the short-term (four fewer events and one more re-TURP per 1000 participants, respectively), compared to M-TURP [325]. An RCT based meta-analysis has shown that TURis reduces the risk of TUR-syndrome and the need for blood transfusion compared to M-TURP [330]. It was concluded that TURis is associated with improved peri-operative safety, eliminating the risk of TUR-syndrome, reducing the risk of blood transfusion/clot retention and hospital stay. No significant difference was detected in urethral stricture rates.

Data from the vast majority of individual RCTs with mid- to long-term follow-up (up to 60 months), showed no differences between M-TURP and B-TURP in urethral stricture/BNC rates [331-339], in accordance with all published meta-analyses. However, two individual RCTs have shown opposing results [338, 344]. A significantly higher stricture (urethral stricture + BNC) rate was detected in the B-TURP arm performed with a "quasi" bipolar system (TURis, Olympus Medical) in patients with a prostate volume > 70 mL at 36-months follow-up [338]. In addition, a significantly higher BNC, but not urethral stricture, rate was detected in the B-TURP arm performed with a "true" bipolar system (Gyrus PK SuperPulse, Olympus Medical) in 137 patients at twelve months follow-up [344].

Randomised controlled trials using the erectile function domain of the IIEF (IIEF-ED) and the ejaculatory domain of the male sexual-health questionnaire (Ej-MSHQ) showed that M-TURP and B-TURP have a similar effect on erectile and ejaculatory function [345, 346]. Comparative evaluations of the effects on overall sexual function, quantified with IIEF-15, showed no differences between B-TURP and M-TURP at twelve months follow-up (erection, orgasmic function, sexual desire, intercourse satisfaction, overall satisfaction) [346, 347]. Furthermore, the largest meta-analysis published to date, showed that erectile function measured by IIEF-5 appears to be similar at twelve months follow-up after B-TURP and M-TURP [325].

A comparative study [348] evaluated the safety of B-TURP in patients taking therapeutic oral anticoagulation (phenprocoumon) or anti-platelet drug therapy (acetylsalicylic acid or clopidogrel), without stopping or bridging the medication. Outcomes under acetylsalicylic acid were comparable to the unmedicated control group. Under oral anticoagulation therapy catheterisation (median 41-hours vs. 24-hours) and hospitalisation time was longer (median four days vs. three days), AUR rate was higher (18% vs. 6%), but blood transfusion rates did not differ to the control group. Under anti-platelet therapy blood transfusion (19% vs. 1%) and re-hospitalisation rates (19% vs. 3%) were higher.

Practical considerations: Monopolar-TURP is an effective treatment for moderate-to-severe LUTS secondary to BPO. The choice should be based primarily on prostate volume (30-80 mL suitable for M-TURP). No studies on the optimal cut-off value exist, but the complication rates increase with prostate size [342]. The upper limit for M-TURP is suggested as 80 mL (based on Panel consensus, under the assumption that this limit depends on the surgeon's experience, choice of resectoscope size and resection speed), as surgical duration increases, there is a significant increase in the rate of complications and the procedure is safest when performed in under 90 minutes [349].

Bipolar TURP in patients with moderate-to-severe LUTS secondary to BPO has similar efficacy with M-TURP but lower peri-operative morbidity. The duration of improvements with B-TURP were documented in a number of RCTs with mid-term follow-up. Long-term results (up to five years) for B-TURP showed that safety and efficacy are comparable to M-TURP [331-339]. The choice of B-TURP should be based on equipment availability, surgeon's experience, and patient's preference.

Summary of evidence	**LE**
Bipolar- or M-TURP is the current standard surgical procedure for men with prostate sizes of 30-80 mL and bothersome moderate-to-severe LUTS secondary of BPO.	1a
Bipolar-TURP achieves short-, mid- and long-term results comparable with M-TURP, but B-TURP has a more favourable peri-operative safety profile.	1a

Recommendation	**Strength rating**
Offer bipolar- or monopolar-transurethral resection of the prostate to surgically treat moderate-to-severe LUTS in men with prostate size of 30-80 mL.	Strong

5.3.1.2 Holmium laser resection of the prostate

With the advent of holmium laser enucleation of the prostate (section 5.3.2.3) and the fact that no relevant publications on holmium laser resection of the prostate (HoLRP) have been published since 2004, HoLRP of the prostate does not play a role in contemporary treatment algorithms.

5.3.1.3 Thulium:yttrium-aluminium-garnet laser vaporesection of the prostate

Mechanism of action: In the *Thulium:yttrium-aluminium-garnet laser* (Tm:YAG), a wavelength between 1,940 and 2,013 nm is emitted in continuous wave mode. The laser is primarily used in front-fire applications [350]. Different applications such as vaporesection (ThuVARP) have been published [351].

Efficacy: Several meta-analyses with pooled data from both RCTs, and non-RCTs have evaluated ThuVARP vs. M-TURP [352-354], and B-TURP [355-357]. The largest meta-analyses included nine RCTs and seven non-RCTs and reported no clinically relevant differences in efficacy (IPSS, QoL score and Q_{max}) between ThuVARP and M-TURP or B-TURP at twelve months [356]. A multicentre, RCT with 410 men reported that ThuVARP and TURP are equivalent in terms of IPSS but not Q_{max}, with TURP deemed superior at twelve months follow-up [358]. The beneficial effect of TURP in terms of Q_{max} was strengthened in men aged < 70 years and in those diagnosed with LUTS rather than urinary retention. No differences in individual patient-reported urinary symptoms were seen between arms, with the exception of some evidence to indicate potential reduction in nocturia in the TURP arm. Data from one RCT with long-term follow-up showed no difference in efficacy and re-operation rates between ThuVARP and M-TURP (2.1% vs. 4.1%, respectively) [359]. A prospective multicentre study on ThuVARP, including 2,216 patients, showed durable post-operative improvement in IPSS, QoL, Q_{max}, and PVR for the entire eight years of follow-up [360].

Tolerability and safety: In a number of meta-analyses longer operation times, shorter catheterisation/ hospitalisation times and less blood loss without significant differences in transfusion rates or in any other short-term complication rates have been reported for ThuVARP compared to TURP [352-357]. A significantly higher transfusion rate was reported after M-TURP in two meta-analyses [354, 356]. However, overall RCT quality

was relatively low with limited follow-up potentially accounting for under-reporting of late complications, such as urethral stricture/BNC [356]. A multicentre RCT with 410 men, followed up for twelve months reported that ThuVARP and TURP show similar operation, catheterisation, and hospitalisation times between arms with no difference in the frequency or severity of surgical complications or in blood transfusions rate or haemoglobin change [358, 361]. Patients with urinary retention had similarly positive outcomes to those with LUTS [358, 361]. Data from three RCTs with mid- to long-term follow-up (18 to 48 months) showed no differences in late complication rates between ThuVARP and TURP [359, 362, 363].

Haemoglobin drop was significantly higher in the bridging group in a retrospectively analysed case series of 103 patients who underwent ThuVARP and received either low molecular weight heparin bridging or continued antiplatelet/anticoagulant therapy [364].

Practical considerations: As a limited number of RCTs with mid- to long-term follow-up support the efficacy of ThuVARP, there is a need for ongoing investigation of the technique.

Summary of evidence	**LE**
Laser vaporesection of the prostate using Tm:YAG laser (ThuVARP) has similar operation, catheterisation and hospitalisation times compared to TURP. ThuVARP and TURP are equivalent in terms of IPSS but not Q_{max}, with TURP deemed superior at twelve months follow-up. ThuVARP and TURP show similar short-term safety. Mid- to long-term results on efficacy and safety compared to TURP are very limited.	1b

Recommendation	**Strength rating**
Offer laser resection of the prostate using Tm:YAG laser (ThuVARP) as an alternative to TURP.	Weak

5.3.1.4 Transurethral incision of the prostate

Mechanism of action: Transurethral incision of the prostate (TUIP) involves incising the bladder outlet without relevant tissue removal. Transurethral incision of the prostate is conventionally performed with Collins knife using electrocautery; however, alternative energy sources such as holmium laser may be used [365]. The mainstay of this technique is in prostate sizes < 30 mL without a middle lobe.

Efficacy: An RCT comparing conventional TUIP vs. TUIP using holmium laser in prostates ≤ 30 mL with a follow-up of twelve months, found both procedures to be equally effective in relieving BOO with similarly low re-operation rates [365]. A meta-analysis of ten RCTs found similar LUTS improvements and lower but significant improvements in Q_{max} for TUIP [366]. 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 meta-analysis of six trials showed that re-operation was more common after TUIP (18.4%) than after M-TURP (7.2%) [366].

Tolerability and safety: An RCT comparing conventional TUIP vs. TUIP using holmium laser reported both procedures to be safe with low complication rates; however, the operation time and retrograde ejaculation rate was significantly lower in the conventional TUIP arm [365]. No cases of TUR-syndrome have been recorded after TUIP. The risk of bleeding after TUIP is small [366].

Practical considerations: Transurethral incision of the prostate is an effective treatment for moderate-to-severe LUTS secondary to BPO. The choice between M-TURP and TUIP should be based primarily on prostate volume (< 30 mL TUIP) [366].

Summary of evidence	**LE**
Transurethral incision of the prostate shows similar efficacy and safety to M-TURP for treating moderate-to-severe LUTS secondary to BPO in men with prostates < 30 mL.	1a
No case of TUR-syndrome has been recorded, the risk of bleeding requiring transfusion is negligible and retrograde ejaculation rate is significantly lower after TUIP, but the re-operation rate is higher compared to M-TURP.	1a
The choice between TUIP and TURP should be based primarily on prostate volume (< 30 mL and 30-80 mL suitable for TUIP and TURP, respectively).	4

Recommendation	Strength rating
Offer transurethral incision of the prostate to surgically treat moderate-to-severe LUTS in men with prostate size < 30 mL, without a middle lobe.	Strong

*5.3.2 **Enucleation of the prostate***

5.3.2.1 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: Open prostatectomy reduces LUTS by 63-86% (12.5-23.3 IPSS points), improves QoL score by 60-87%, increases mean Q_{max} by 375% (+16.5-20.2 mL/s), and reduces PVR by 86-98%. Efficacy is maintained for up to six years [367-372]. Data from an Austrian nationwide study of 2,452 men submitted to OP showed that the endourological re-intervention rates after primary OP were 0.9%, 3.0%, 6.0%, and 8.8%, at three months, one year, five years, and eight years, respectively [323].

Two meta-analyses [373, 374] evaluated the overall efficacy of OP performed via a transvesical approach vs. two transurethral enucleation techniques for treating patients with large glands, namely bipolar transurethral enucleation of the prostate (B-TUEP) and holmium laser enucleation of the prostate (HoLEP). Five RCTs compared OP with B-TUEP [372, 375-378] and four RCTs compared OP with HoLEP [367, 368, 379, 380]. At three, six, twelve and 24-months follow-up there were no significant differences in Q_{max} [374]. Post-void residual, PSA, IPSS and QoL score showed no significant differences during twelve-months follow-up [374]. Open prostatectomy and HoLEP had similar improvements regarding Q_{max}, IPSS score and re-operation rates after five years in one RCT [367].

Tolerability and safety: Two meta-analyses evaluated the overall safety of OP performed via a transvesical approach vs. B-TUEP and HoLEP [373, 374]. Operation time did not differ significantly between OP and B-TUEP but was significantly shorter for OP compared to HoLEP. Catheterisation and hospitalisation time were significantly longer for OP, which was also associated with more blood transfusions. There were no significant differences regarding other complications. There was no significant difference in IIEF-5 at three, six, twelve and 24-months follow-up.

Open prostatectomy mortality has decreased significantly during the past two decades (< 0.25%) [371, 381]. Data from a study of 1,286 men submitted to OP showed mortality rates of 0.2% at 30 days and 0.4% at 90 days [324].

The estimated transfusion rate was about 7-14% [367, 370, 371, 373] Long-term complications include transient UI (up to 10%), BNC and urethral stricture (about 6%) [367-369, 373, 382].

Practical considerations: Open prostatectomy is the most invasive surgical method, but it is an effective and durable procedure for the treatment of LUTS/BPO. In the absence of an endourological armamentarium including a holmium laser or a bipolar system and with appropriate patient consent, OP is a reasonable surgical treatment of choice for men with prostates > 80 mL.

Summary of evidence	LE
Open prostatectomy is an effective and durable procedure for the treatment of LUTS/BPO, but it is the most invasive surgical method.	1b
Open prostatectomy shows similar short- and mid-term efficacy to B-TUEP and HoLEP for treating moderate-to-severe LUTS secondary to BPO in patients with large prostates.	1a
Open prostatectomy has a less favourable peri-operative safety profile compared to B-TUEP and HoLEP.	1a
The long-term functional results of OP are comparable to HoLEP.	1b

Recommendation	Strength rating
Offer open prostatectomy in the absence of anatomical endoscopic enucleation of the prostate to treat moderate-to-severe LUTS in men with prostate size > 80 mL.	Strong

5.3.2.2 Bipolar transurethral enucleation of the prostate

Mechanism of action: Following the principles of bipolar technology (section 5.3.1.1), the obstructive adenoma is enucleated endoscopically by the transurethral approach. Currently, two technologies exist, namely plasmakinetic (PK) enucleation of the prostate (PKEP) and bipolar plasma enucleation of the prostate (BPEP) [378, 383, 384]. Bipolar transurethral enucleation of the prostate is followed by either morcellation [378, 385] or resection [383, 386-390] of the enucleated adenoma.

Efficacy: Two meta-analyses, reported similar efficacy at twelve months in terms of IPSS, QoL score and Q_{max} for B-TUEP (PKEP or BPEP) vs. B-TURP [391, 392]. Another meta-analysis evaluating B-TUEP vs. B-TURP, reported similar efficacy at 36 months in terms of IPSS, and Q_{max} [340]. One RCT evaluating PKEP vs. M-TURP reported a significant improvement in IPSS, QoL score, and Q_{max}, with urodynamically proven de-obstruction favouring PKEP at 36-months follow-up [387]. One RCT evaluating PKEP vs. B-TURP in patients with prostate volume > 80 mL reported no clinically relevant differences in IPSS, QoL score, and Q_{max}, at six months follow up [393]. Another RCT evaluating BPEP vs. B-TURP in patients with prostate volume > 80 mL reported not clinically relevant differences in IPSS, QoL score, Q_{max} and PVR at 24-months follow-up [394] Two RCTs evaluated the mid-term efficacy of PKEP vs. B-TURP at 36 months [388, 389] and one RCT evaluated long-term efficacy at 60 months [390]. Efficacy was significantly better for PKEP in patients with large prostates at 36, 48 and 60 months [388, 390]. Comparative data on efficacy for B-TUEP vs. OP and the various forms of laser enucleation are presented in section 5.3.2.1 – 5.3.2.5, respectively.

Tolerability and safety: Two meta-analyses evaluating B-TUEP vs. B-TURP reported similar operation, catheterisation and hospitalisation times; lower acute urine retention rates; significantly reduced haemoglobin drop and blood transfusion rates; no difference in ED; and no difference in all other reported complication rates including urethral stricture/BNC rates for B-TUEP at 24-months follow-up [391, 392]. [394]. A meta-analyses evaluating PKEP vs. TURP reported that mid-term IIEF-5 scores were comparable [395]. Another meta-analyses reported less bleeding with B-TUEP compared to M-TURP but similar UI rates and AUR after catheter removal [340]. An RCT evaluating PKEP vs. M-TURP in patients with prostate volume < 80 mL and 36-month follow-up reported that PKEP is superior to M-TURP in terms of catheterisation, and hospitalisation time [387]. No significant differences between the arms were reported in operation time, blood transfusion rates, sexual function, or any other reported complications (TUR-syndrome, clot retention, incontinence, retrograde ejaculation, urethral structures/BNC) [387]. One RCT evaluating PKEP vs. B-TURP in patients' prostate volume > 80 mL and six months follow-up reported that PKEP is superior to B-TURP in terms of operation, catheterisation and hospitalisation time [393]. Significant differences were reported in blood transfusion, BNC and retrograde ejaculation rates favouring PKEP, but no differences in urethral stricture and ED rates were reported [393]Another RCT evaluating BPEP vs. B-TURP in patients with prostate volume > 80 mL reported that BPEP had longer operative time but shorter catheterisation, hospitalisation time with no differences in blood transfusion, urethral stricture and UI rates at 24-months follow-up [394]. No difference in urethral stricture/BNC rates was reported at 60 months follow-up [390]. Comparative data on efficacy for B-TUEP vs. OP and the various forms of laser enucleation are presented in section 5.3.2.1 – 5.3.2.5, respectively.

Summary of evidence	**LE**
Bipolar transurethral PKEP shows favourable mid- to long-term efficacy compared to TURP.	1b
Bipolar transurethral PKEP has a favourable peri-operative safety profile and demonstrates similar mid- to long-term safety compared to TURP.	1b

Recommendation	**Strength rating**
Offer bipolar transurethral (plasmakinetic) enucleation of the prostate to men with moderate-to-severe LUTS as an alternative to transurethral resection of the prostate.	Weak

5.3.2.3 Holmium laser enucleation 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 [396].

Efficacy: An initial meta-analyses reported no significant differences in short-term efficacy (Q_{max}) and re-intervention rates (4.3% vs. 8.8%) between HoLEP and M-TURP [397]; however, subsequent meta-analyses reported favourable short-term efficacy (Q_{max} and IPSS) for HoLEP [320, 353, 391, 398]. Meta-analyses reported similar efficacy at 24-months in terms of IPSS, and Q_{max} [340]. Three meta-analyses evaluating HoLEP vs.

B-TURP showed no significant differences in short-term efficacy (IPSS, QoL score and Q_{max}) [340, 391, 399]. One RCT comparing HoLEP with B-TURP in patients with prostate volume < 80 mL reported no significant difference in IPSS, QoL score and Q_{max} at 24-months [400]. One RCT comparing HoLEP with M-TURP in a small number of patients with mean prostate volume < 80 mL and a seven year follow-up found that the functional long-term results were comparable [396]. Another RCT comparing HoLEP with B-TURP in patients with prostate volume > 80 mL reported no significant difference in IPSS, QoL score and Q_{max} at 36 months, however, the overall re-treatment rate was significantly lower following HoLEP with less patients restarting α-blockers and less re-operations [401]. Comparative efficacy data for HoLEP vs. OP is presented in section 5.3.2.1. One RCT evaluating HoLEP vs. PKEP in patients with mean prostate volume < 80 mL reported similar improvements in IPSS and Q_{max} at twelve months follow-up [385]. In another RCT comparing HoLEP with PkEP improvements of IPSS, QoL, PVR, and Q_{max} were stable at 3-year follow-up without differences between the groups [402, 403].

An RCT comparing HoLEP vs. bipolar transurethral enucleation reported no significant difference in IPSS, QoL score, PVR, and Q_{max} at one, three-, and twelve-months follow-up [404].

A SR and meta-analysis based on retrospective series, revealed a superior enucleation efficiency associated with *en-bloc* and the two-lobe techniques compared to the three-lobe technique, but no superiority on functional outcomes were reported [405].

Tolerability and safety: Several meta-analyses found that HoLEP has longer operation times, shorter catheterisation and hospitalisation times, reduced blood loss, fewer blood transfusions but no significant differences in urethral strictures (2.6% vs. 4.4%) and stress urinary incontinence (SUI) (1.5% vs. 1.5%) rates compared to M-TURP [353, 391, 397, 398, 406]. Another meta-analysis reported that HoLEP has shorter catheterisation times, fewer blood transfusions, urethral strictures and UTIs but no significant differences in clot retention rates and AUR after catheter removal compared to M-TURP [340]. Three meta-analyses evaluated HoLEP vs. B-TURP [391, 399, 407]. One, reported longer operation times for HoLEP, but no significant differences in hospitalisation time or complication rates [391] whilst another reported no significant differences in operation and catheterisation times or short-term complication rates [399]. Data from a large national database on peri-operative outcomes of 2,869 laser enucleation of the prostate and 37,577 TURP procedures supports that laser enucleation of the prostate is associated with longer operation times, shorter hospitalisation times, similar complication rates (including transfusions, and re-operations), but lower rates of infectious complications [408]. A SR reported that HoLEP has lower AUR rates after catheter removal but similar haemoglobin drop, UTI, urethral stricture, and UI rates [340]. An RCT comparing HoLEP with B-TURP in patients with prostate volume < 80 mL reported longer operation time, shorter catheterisation and hospitalisation times and a lower risk for haemorrhage for HoLEP with no significant differences in blood transfusion rates or other complication rates at 24 months [400]. Another RCT comparing HoLEP with B-TURP in patients with prostate volume > 80 mL reported shorter operation, catheterisation and hospitalisation times and lower blood transfusion rates for HoLEP but no differences in complication rates including UI and IIEF-5 score at 36 months [401]Comparative data on safety of HoLEP vs. OP are presented in section 5.3.2.1. One RCT evaluating HoLEP vs. PKEP in patients with mean prostate volume < 80 mL reported significantly shorter operation times for HoLEP, but similar catheterisation and hospitalisation times and complication rates at twelve months follow-up [385]. Another RCT comparing HoLEP with PkEP found a higher haemoglobin drop and a prolonged haematuria in the PkEP group but no clinical significant blood loss in either arm occurred [402, 403]. An RCT comparing HoLEP vs. bipolar B-TUEP demonstrated shorter operation and hospitalisation times and earlier catheter removal for HoLEP [404].

Another RCT comparing high (2J, 50 Hz) with medium power (2J, 30 Hz) HoLEP demonstrated comparable peri-operative safety and long-term durability [409].

A double-blind RCT of pulse modulation use in HoLEP (Virtual basket) demonstrated statistically significantly outcomes related to haemostasis (18 vs. 29 min, $p < 0.01$) and operation time (101 vs. 126 min, $p < 0.01$), when compared to conventional HoLEP [410]. This was confirmed in a SR and meta-analysis of seven studies comparing pulse modulation use with standard HoLEP. Shorter enucleation, better haemostasis and shorter total surgical time was found with pulse modulating HoLEP [411].

One RCT evaluating tranexamic acid use in HoLEP surgery did not find any difference with regard to bleeding complications and peri-operative safety [412].

Holmium laser enucleation of the prostate has been safely performed in patients using anticoagulant and/or antiplatelet medications. However, current limitations include: a lack of RCTs; limited data on short- and mid-term complications and bridging therapy; data presentation does not allow for separate interpretation of either antiplatelet and anticoagulant therapy [413].

A meta-analysis of seven RCTs evaluating HoLEP vs. TURP reported that short- and mid-term IIEF-5 scores were comparable, whilst long-term scores were significantly better for HoLEP [414]. Two other meta-analyses detected no difference in mid-term retrograde ejaculation rates [415].

The impact on erectile function is comparable [416, 417] however the conclusion that retrograde ejaculation is also comparable between HoLEP and TURP is highly dependent on the use template [416, 417]. Erectile function did not decrease from baseline in either group; three quarters of sexually active patients had retrograde ejaculation after HoLEP. Data have shown that ejaculation and orgasm perception are the two most impacted domains after HoLEP [418]. Attempts to maintain ejaculatory function with HoLEP have been reported to be successful in up to 46.2% of patients [419].

An RCT comparing HoLEP vs. B-TUEP, reported shorter operation and hospitalisation times and earlier catheter removal for HoLEP [404].

Practical considerations: The experience of the surgeon is the most important factor affecting the overall occurrence of complications in HoLEP [420, 421]. Mentorship programmes are advised to improve surgical performance from both an institutional and personal learning curve perspective [422-424]. Pulse modulation use in HoLEP (Virtual basket) demonstrated statistically significantly outcomes related to haemostasis and operation times, clinical and health economic benefits remains to be determined.

Summary of evidence	**LE**
Laser enucleation of the prostate using Ho:YAG laser (HoLEP) demonstrates similar mid- to long-term efficacy when compared to TURP.	1b
Laser enucleation of the prostate using Ho:YAG laser (HoLEP) demonstrates similar short-term safety when compared to TURP.	1a
Laser enucleation of the prostate using Ho:YAG laser (HoLEP) demonstrates longer operation times, but a more favourable peri-operative profile when compared to TURP.	1a

Recommendation	**Strength rating**
Offer laser enucleation of the prostate using Ho:YAG laser (HoLEP) to men with moderate-to-severe LUTS as an alternative to transurethral resection of the prostate or open prostatectomy.	Strong

5.3.2.4 Thulium:yttrium-aluminium-garnet laser enucleation of the prostate

Mechanism of action: The Tm:YAG laser has been described in section 5.3.1.3. Enucleation using the Tm:YAG laser includes thulium vapoenucleation of the prostate (ThuVEP) and thulium Laser enucleation of the prostate (ThuLEP) (blunt enucleation). (Super) pulsed or continuous wave (CW) thulium:yttrium-aluminium garnet (wavelength 2,013 nm) or thulium fibre lasers (wavelength 1,940 nm) are be used for laser enucleation of the prostate and are well absorbed by water and water-containing tissues.

Efficacy: Two meta-analyses evaluating ThuLEP vs. M-TURP and B-TURP reported no clinically relevant differences in short-term efficacy (Q_{max}, IPSS and QoL score) [340, 391]. An RCT with five years follow-up comparing ThuLEP with B-TURP found no difference between the two procedures for Q_{max}, IPSS, PVR, and QoL [425]. A meta-analysis [426] evaluating ThuLEP vs. HoLEP showed no clinically relevant differences in IPSS, QoL score and Q_{max} at twelve months in accordance with one RCT showing similar results at eighteen months [427]. Furthermore, ThuLEP and PKEP were compared in one RCT with twelve months follow-up with no difference with regard to efficacy [428]. There are mainly prospective case studies on ThuVEP showing a significant improvement in IPSS, Q_{max}, and PVR after treatment [429-432]. In a retrospective comparative series, there were no differences between (super)pulsed and CW ThuLEP with regard to intra-operative, peri-operative data and clinical efficacy (Q_{max}, IPSS, QoL) [433].

Tolerability and safety: Two meta-analyses evaluating ThuLEP vs. M-TURP and B-TURP reported a longer operation time and shorter catheterisation time for ThuLEP compared to M-TURP and a shorter hospitalisation time for ThuLEP compared to B-TURP [340, 391]. Lower blood transfusion rates compared to M-TURP, lower clot retention rates compared to B-TURP, and no difference in the other complication rates were also reported for ThuLEP [340, 391]. One meta-analysis [426] evaluating ThuLEP vs. HoLEP showed a significant difference in enucleation time favouring ThuLEP, but no significant differences in operation, catheterisation and hospitalisation times, and short-term complication rates. One RCT showed no urethral and bladder neck strictures at eighteen months after ThuLEP and HoLEP, respectively [427]. ThuLEP and PKEP were compared in one RCT with twelve months follow-up [428]. No significant difference in complication rates was detected, but haemoglobin level decrease and catheterisation time was significantly lower for ThuLEP. An RCT comparing ThuLEP with B-TURP reported a significant difference in IIEF-5 score favouring ThuLEP at twelve months [434].

In comparative studies ThuVEP shows high intra-operative safety [435], also in case series of patients with large prostates [429] and anticoagulation or bleeding disorders [430, 431]. A study focusing on post-operative complications after ThuVEP reported adverse events in 31% of cases, with 6.6% complications greater then Clavien grade 2 [436]. 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% [431].

Practical considerations: ThuLEP seems to offer similar efficacy and safety when compared to TURP, bipolar enucleation and HoLEP; whereas, ThuVEP is not supported by RCTs. Based on the limited number of RCTs there is a need for ongoing investigation of these techniques [437, 438].

Summary of evidence	LE
Enucleation of the prostate using the Tm:YAG laser demonstrates similar efficacy when compared to M-TURP/bipolar transurethral (plasmakinetic) enucleation, HoLEP and B-TURP in the short-, mid-, and long-term, respectively.	1b
Enucleation of the prostate using the Tm:YAG laser (ThuLEP) demonstrates similar safety compared to TURP/bipolar transurethral (plasmakinetic) enucleation, and HoLEP in the short- and mid-term, respectively.	1b
Vapoenucleation of the prostate using a Tm:YAG laser (ThuVEP) seems to be safe in patients with large prostates and those receiving anticoagulant or antiplatelet therapy.	2b

Recommendations	Strength rating
Offer enucleation of the prostate using the Tm:YAG laser (ThuLEP, ThuVEP) to men with moderate-to-severe LUTS as an alternative to transurethral resection of the prostate, holmium laser enucleation or bipolar transurethral (plasmakinetic) enucleation.	Weak
Offer Tm:YAG laser enucleation of the prostate to patients receiving anticoagulant or antiplatelet therapy.	Weak

5.3.2.5 Diode laser enucleation 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 [439].

Efficacy: One RCT comparing 1,318 nm diode laser enucleation of the prostate (DiLEP) with B-TURP in patients with mean prostate volume < 80 mL reported no significant differences in IPSS, QoL score, Q_{max} and PVR at six months follow-up [440]. Another RCT comparing 1,470 nm DiLEP with B-TURP in patients with mean prostate volume < 80 mL also reported no significant differences in IPSS, QoL score, Q_{max} and PVR at twelve months follow-up [441]. In addition, three RCTs comparing 980 nm DiLEP with PKEP in patients with mean prostate volume < 80 mL [442, 443] and > 80 mL [444] reported no significant differences in IPSS, QoL score, Q_{max} and PVR at twelve months follow-up. An RCT of DilEP (980 nm) vs. HoLEP detected no significant difference in Q_{max}, PVR, IPSS, and QoL within twelve months follow-up [445].

Tolerability and safety: One small RCT comparing 1,318 nm DiLEP with B-TURP in patients with mean prostate volume < 80 mL and six months follow-up reported a significantly longer operation time for DiLEP, but shorter catheterisation and hospitalisation times, as well as less blood loss (without differences in blood transfusion rates) [440]. No differences in complication rates were reported between the two arms [440]. Another RCT comparing 1,470 nm DiLEP with B-TURP in patients with prostate volume < 80 mL and twelve months follow-up reported significantly shorter operation, catheterisation, and hospitalisation times with less blood loss (without differences in blood transfusion rates) for DiLEP, with no differences in complication rates between the two arms [441]. Three RCTs comparing 980 nm DiLEP with PKEP in patients with prostate volume < 80 mL [442, 443] and > 80 mL [444] and twelve months follow-up reported conflicting peri-operative outcomes. All trials reported no differences in blood transfusion rates and complication rates [442-444].

An RCT of DiLEP (980 nm) vs. HoLEP with twelve months follow-up demonstrated no significant difference in peri-operative outcomes including operation and hospitalisation times [445].

Practical considerations: Diode laser enucleation seems to offer similar efficacy and safety when compared to either B-TURP or bipolar transurethral (plasmakinetic) enucleation. Based on the limited number of mainly low-quality RCTs, and controversial data on the retreatment rate, results for DiLEP should be evaluated in further higher quality RCTs.

Summary of evidence	LE
Laser enucleation of the prostate using the 1,318 nm or 1,470 laser showed comparable short-term efficacy and safety to B-TURP. Peri-operative parameters like blood loss, catheterisation time and hospital stay are in favour of diode enucleation.	1b
Laser enucleation of the prostate using the 980 nm laser showed comparable short-term efficacy and safety to bipolar transurethral (plasmakinetic) enucleation.	1b

Recommendation	Strength rating
Offer 120-W 980 nm, 1,318 nm or 1,470 nm diode laser enucleation of the prostate to men with moderate-to-severe LUTS as a comparable alternative to bipolar transurethral (plasmakinetic) enucleation or bipolar transurethral resection of the prostate.	Weak

5.3.2.6 Enucleation techniques under investigation

5.3.2.6.1 Minimal invasive simple prostatectomy

Mechanism of action: The term minimal invasive simple prostatectomy (MISP) includes laparoscopic simple prostatectomy (LSP) [446] and robot-assisted simple prostatectomy (RASP) [447]. Both LSP and RASP are performed using different personalised techniques, based on the transcapsular (Millin) or transvesical (Freyer) approach.

Efficacy: A SR and meta-analyses showed that in 27 observational studies including 764 patients mean increase in Q_{max} was 14.3 mL/s, and the mean improvement in IPSS was 17.2 [448]. There were no differences in improvements in Q_{max} and IPSS [448]. A meta-analysis comparing MISP vs. OP reported no significant differences with regard to functional and symptom parameters between the two techniques [449]. A multicentre RCT with median follow-up of 26 months did not demonstrate any significantly different functional or peri-operative results between LSP, RASP and HoLEP [450]. A SR and meta-analysis of five non-randomised comparative trials comparing RASP with LSP demonstrated a shorter length of hospital stay after RASP as well as a higher post-operative Q_{max} [451, 452]. An RCT comparing HoLEP versus MISP for large volume (≥ 120 mL) prostate glands resulted in longer catheterisation time, in the LSP group than RASP and HoLEP groups (p=0.002). Furthermore, MISP resulted in longer hospitalisation, and lower rate of patients with new-onset of storage LUTS [452].

Tolerability and safety: A meta-analysis comparing MISP vs. OP demonstrated shorter hospital stay, as well as blood loss and transfusion rates for MISP [449, 453]. In In comparative studies to OP, length of hospital stay, length of catheter use, and estimated blood loss were significantly lower in the MISP group, while the duration of surgery was longer. There were no differences in peri-operative complications between both procedures [448]. In a multicentre RCT comparing LSP, RASP and HoLEP LSP demonstrated significantly longer catheterisation times than RASP and HoLEP, whilst RASP and LSP showed longer hospitalisation times and lower rates of *de novo* bladder storage symptoms [450]. In a comparative analysis of robotic vs. OP for large-volume prostates, a propensity score-matched analysis was performed with five covariates. Robotic compared with OP demonstrated a significant shorter average length of hospital stay, but longer mean operative time. The robotic approach was associated with a lower estimated blood loss. Improvements in maximal flow rate, IPSS, QoL, PVR and post-operative PSA levels were similar for both groups. There was no difference in complications between the groups [454].

Practical considerations: Currently, most studies on MISP are of a retrospective nature. Adequately powered RCT against reference options are needed to compare efficacy, safety, and hospitalisation times, learning curve and costs of MISP and both OP and endoscopic methods.

Summary of evidence	LE
Minimal invasive simple prostatectomy is feasible in men with prostate sizes > 80 mL needing surgical treatment; however, RCTs are needed.	2a

5.3.2.6.2 532 nm ('Greenlight') laser enucleation of the prostate

Two approaches for Potassium-Titanyl-Phosphate (KTP) and the lithium triborate (LBO) laser-based enucleation technique exist [455]. GreenLEP is an anatomical enucleation technique following the principle of blunt dissection of the adenoma with the sheath and laser energy for incision as described for ThuLEP [456]. A variation is the *in-situ* vaporisation of apically enucleated tissue, also referred to as anatomic vaporisation-

incision technique [456, 457]. To date, no high quality adequate RCTs evaluating enucleation using the KTP/LBO laser have been carried out [458, 459].

*5.3.3 **Vaporisation of the prostate***

5.3.3.1 Bipolar transurethral vaporisation of the prostate

Mechanism of action: Mechanism of action: Bipolar transurethral vaporisation of the prostate (B-TUVP) utilises a bipolar electrode and a high-frequency generator to create plasma field (thin layer of highly ionised particles) to vaporise prostatic tissue [460]. Bipolar transurethral vaporisation of the prostate displays thinner (< 2 mm) coagulation zones [461], compared to monopolar TUVP (up to 10 mm) [462], potentially resulting in fewer irritative side-effects and SUI [461, 463, 464].

Efficacy: Bipolar-TUVP has been compared to TURP in thirteen RCTs, including a total of 1,244 men with a prostate size of < 80 mL [334, 465-476]. Early RCTs evaluated the PK B-TUVP system [465-469]; however, during the last decade, only the "plasma" B-TUVP system with the "mushroom- or button-like" electrode (Olympus, Medical) has been evaluated [334, 470-476]. Results have been pooled in three meta-analyses [320, 477, 478], and a narrative synthesis has been produced in two SRs [320, 479].

Follow-up in most RCTs is twelve months [465-468, 470-472, 474, 476] with the longest being 36 months in a small RCT (n = 40) and eighteen months in a subsequent RCT (n = 340); evaluating PK [469] and plasma B-TUVP [334], respectively. Pooled results from meta-analyses concluded that no significant differences exist in short-term efficacy (IPSS, QoL score, Q_{max} and PVR) between PK B-TUVP and TURP [320, 340, 478] and this was confirmed in a separate SR of seven RCTs [479]. However, the promising initial efficacy profile of the former may be compromised by inferior clinical outcomes (IPSS and Q_{max}) at mid-term. Higher quality RCTs with longer follow-up are necessary to draw definite conclusions on mid and long-term outcomes [320, 469].

Tolerability and safety: Early pooled results concluded that no statistically significant differences exist for intra-operative and short-term complications between PK B-TUVP and TURP, but peri-operative complications are significantly fewer after B-TUVP [320]. However, the results of a statistical analysis comparing pooled specific complication rates were not directly reported in this meta-analysis [320]. Mid-term complications (urethral stricture, ED, and retrograde ejaculation) are similar [469], but larger RCTs with longer follow-up are necessary to draw definite conclusions [320, 469]. A SR of seven RCTs comparing PK and plasma B-TUVP with TURP concluded that most RCTs shorter catheterisation (42.5 vs. 77.5 hours) and hospitalisation times (3.1 vs. 4.4 days) with B-TUVP [479], but another SR concluded that heterogeneity of RCTs, and methodological limitations do not permit firm conclusions [320]. A meta-analysis reported that B-TUVP has shorter and similar catheterisation time compared to M-TURP and B-TURP, respectively; significantly fewer clot retentions/blood transfusions compared to M-TURP but not B-TURP; and no difference in other complication rates compared to either TURP technique [340]. A meta-analysis of six RCTs specifically evaluating plasma B-TUVP vs. TURP, concluded that no significant differences exist between the techniques in overall complication and transfusion rates [478]. However, a statistically significant difference was detected in major complication rates (Clavien 3, 4), including urethral stricture, severe bleeding necessitating re-operation and UI, and in the duration of catheterisation, favouring plasma B-TUVP.

Practical considerations: Bipolar-TUVP and PK TUVP have similar short-term efficacy to TURP, but with a favourable short-term safety profile. However, heterogeneity of RCTs, non-standardised techniques and methodological limitations do not permit firm conclusions, and multicentre, long-term RCTs s are needed.

Summary of evidence	**LE**
Bipolar-TUVP and TURP have similar short-term efficacy.	1a
Plasmakinetic B-TUVP has a favourable peri-operative profile, similar mid-term safety but inferior mid-term efficacy compared to TURP.	1a
Plasma B-TUVP has a lower short-term major morbidity rate compared to TURP.	1a

Recommendation	**Strength rating**
Offer bipolar transurethral vaporisation of the prostate as an alternative to transurethral resection of the prostate to surgically treat moderate-to-severe LUTS in men with a prostate volume of 30-80 mL.	Weak

5.3.3.2 532 nm ('Greenlight') laser vaporisation of the prostate

Mechanism of action: The KTP and LBO lasers have been described in section 5.3.2.6.2.

Efficacy: Meta-analyses of RCTs comparing photoselective vaporisation of the prostate (PVP) using the 80-W and 120-W lasers with TURP have reported no difference in Q_{max} and IPSS between 80-W or 120-W PVP and TURP [480, 481]. Another meta-analysis of four RCTs including 559 patients, on the 120-W laser, demonstrated no significant difference in functional and symptomatic parameters at 24-month follow-up when compared to TURP [482]. A meta-analysis of two RCTs reported similar efficacy of 120-W PVP, compared to M-TURP at 36-months follow-up [340].

The only available RCT for the 180-W laser reported non-inferiority to TURP in terms of IPSS, Q_{max}, PVR, prostate volume reduction, PSA decrease and QoL questionnaires. Efficacy outcomes were similar to TURP with stable results at 24-months follow-up [483].

One RCT comparing HoLEP to PVP, in patients with prostates > 60 mL, showed comparable symptom improvement, but significantly higher flow rates and lower PVR volume after HoLEP at short-term follow-up; in addition, PVP showed a 22% conversion rate to TURP [484].

One RCT compared B-TUVP with PVP with the 180-W XPS Laser. Comparable improvement in IPSS and Q_{max} were reported at 24-months follow-up [485].

Tolerability and safety: A meta-analysis of RCTs comparing the 80-W and 120-W lasers with TURP showed shorter catheterisation time (mean difference 32 hours) and length of hospital stay (mean difference 1.85 days) after PVP [320]. Blood transfusions and clot retention were less with PVP. No difference was noted in post-operative urinary retention, UTI, meatal stenosis, urethral stricture, or bladder neck stenosis [320]. A meta-analysis including trials with the 120-W laser likewise reported lower transfusion rates, catheterisation time and duration of hospital stay compared to TURP. Re-operation rates and operation time were in favour of TURP. No significant differences were demonstrated for treatment for urethral stricture, BNC, incidence of incontinence and UTI [482]. A meta-analysis confirmed that PVP was superior to both M-TURP/B-TURP with regard to catheterisation and to M-TURP but not to B-TURP with regard to transfusion rate and clot retention [340]. In an RCT comparing the 120-W HPS laser with TURP, with a follow-up of 36-months, the re-operation rate was significantly higher after PVP (11% vs. 1.8%) [486].

180-W Greenlight laser prostatectomy is non-inferior to TURP in terms of peri-operative complications. Re-operation free survival during a 24-month follow-up was comparable between the TURP-arm and the 180-W XPS laser-arm [483].

A retrospective feasibility study on 537 patients with a median follow-up of 31 months, of which 517 were treated in an outpatient basis, showed that outpatient PVP with the 180-W XPS laser can be performed safely with a low re-admission and complication rate [487].

One retrospective long-term follow up study on 21,869 patients treated in twenty centres in Finland compared short-term and long-term morbidity in patients undergoing monopolar or bipolar TURP or any of the three generations of PVP [488]. Re-operations for bleeding were less frequent after PVP. Cumulative incidence for re-operation was higher after PVP (23.5%) than after TURP in long-term follow-up (17.8%) [488].

Based mostly on case series, the 80-,120- and 180-W Greenlight laser appears to be safe in high-risk patients undergoing anticoagulation treatment [489-492]; however, patients under anticoagulation therapy were either excluded from or represented a very small sample in currently available RCTs. In one study, anticoagulated patients had significantly higher rates of bladder irrigation (17.2%) compared with those not taking anticoagulants (5.4%) [492]. In contrast, another retrospective study focusing on the 180-W LBO laser did not find any significant differences between patients receiving or not receiving anticoagulants [493]. A retrospective study of a mixed cohort of patients, treated with 80-W KTP PVP and 120-W LBO HPS, revealed that delayed gross haematuria was common in patients (33.8%) during an average follow-up of 33 months [494]. A retrospective review of a database of patients undergoing 180-W PVP, without interruption of anticoagulation therapy, had a 30.5% rate of peri-operative adverse events with a significant occurrence of high grade Clavien Dindo events [495].

Safety in patients with urinary retention, impaired detrusor contractility, elderly patients or prostates > 80 mL was shown in various prospective short-term non-randomised trials.

A retrospective study on 1,077 patients [496] with a median eighteen months follow-up, compared the functional results and the safety profile of PVP in patients younger and older than 75 years of age. The authors did not find any differences in terms of complications in older patients, with only 0.6% of Clavien III and an overall complications rate of 29.6%. Data on functional outcomes in the older group of patients, showed amelioration of all parameters from the baseline, with 111.7% of improvement of peak flow and 69.5% of IPSS reduction without statistical differences with the counterparts at twelve months. However this similarity of results disappears by extending the study period up to a median of eighteen months, underlying the fact that younger patients maintain their improvement more than older patients, who nevertheless maintain a relevant improvement compared to their baseline [496].

No RCT including prostates > 100 mL has been reported; therefore, comparison of retreatment rates between prostate volumes of different sizes is not possible [497-499].

A meta-analysis of five RCTs comparing collectively all three "Greenlight" lasers with TURP detected no difference in retrograde ejaculation rates [415]. Additional studies have also reported no difference between OP/TURP and Greenlight PVP for erectile function [500, 501]. However, IIEF-5 scores were significantly decreased at six-, twelve-, and 24- months in patients with pre-operative IIEF-5 greater than nineteen [502].

No significant difference with respect to peri- and post-operative complications was reported in an RCT comparing B-TUVP and PVP with the 180-W XPS Laser. Redo TURP for recurrent adenoma was required in 9.8% (B-TUVP) and 1.7% (PVP) of the patients during 24-months follow-up, respectively [485].

Practical considerations: The 180-W XPS represents the current standard of generators for PVP; however, the number and quality of supporting publications are low, especially for large glands (> 100 mL), with no long-term follow-up.

Summary of evidence	**LE**
Laser vaporisation of the prostate using the 80-W KTP and the 120-W LBO laser (PVP) demonstrated higher intra-operative safety with regard to haemostatic properties when compared to TURP. Peri-operative parameters such as catheterisation time and hospital stay are in favour of PVP, whereas operation time and risk of re-operation are in favour of TURP. Short-term results for the 80-W KTP laser and mid-term results for the 120-W LBO laser were comparable to TURP.	1a
Laser vaporisation of the prostate using the 180-W LBO laser (PVP) demonstrated higher intra-operative safety with regard to haemostatic properties when compared to TURP. Peri-operative parameters such as catheterisation time and hospital stay were in favour of PVP, whereas operation time was in favour of TURP. Short- to mid-term results are comparable to TURP.	1b
Laser vaporisation of the prostate using the 80-W KTP and 120-W LBO lasers seems to be safe for the treatment of patients receiving antiplatelet or anticoagulant therapy.	2
Laser vaporisation of the prostate using the 180-W LBO laser seems to be safe for the treatment of patients receiving antiplatelet or anticoagulant therapy; however, the level of evidence available is low.	3

Recommendations	**Strength rating**
Offer 80-W 532-nm Potassium-Titanyl-Phosphate (KTP) laser vaporisation of the prostate to men with moderate-to-severe LUTS with a prostate volume of 30-80 mL as an alternative to transurethral resection of the prostate (TURP).	Strong
Offer 120-W 532-nm Lithium Borat (LBO) laser vaporisation of the prostate to men with moderate-to-severe LUTS with a prostate volume of 30-80 mL as an alternative to TURP.	Strong
Offer 180-W 532-nm LBO laser vaporisation of the prostate to men with moderate-to-severe LUTS with a prostate volume of 30-80 mL as an alternative to TURP.	Strong
Offer laser vaporisation of the prostate using 80-W KTP, 120- or 180-W LBO lasers for the treatment of patients receiving antiplatelet or anticoagulant therapy with a prostate volume < 80 mL.	Weak

5.3.3.3 Vaporisation techniques under investigation

5.3.3.3.1 Diode laser vaporisation of the prostate

Mechanism of action: Diode lasers with a wavelength of 980 nm are marketed for prostate vaporisation; however, only a few have been evaluated in clinical trials [350].

Efficacy: Two RCTs for 120-W 980 nm diode laser vaporisation vs. M-TURP are available [503, 504]. The first RCT with 24-month follow-up reported similar efficacy (IPSS, Q_{max} and PVR) at one and six months. However, at twelve- and 24-months improvements in IPSS and Q_{max} were significantly in favour of TURP, and repeat TURP was more frequent in the diode laser group [503]. The second RCT reported equivalent results for both interventions at three-month follow-up [504].

Tolerability and safety: A meta-analysis comparing diode laser vaporisation vs. M-TURP reported shorter catheterisation time and lower transfusion rates for diode laser vaporisation [340]. In an RCT reflecting on peri-operative and post-operative complications no significant differences were demonstrated for clot retention, AUR after catheter removal, UUI and UTI [503]. Moreover, for late complications no significant differences could be demonstrated for re-operation rate, urethral stricture, bladder neck sclerosis, *de novo* sexual dysfunction and

mean time of dysuria [503]. Published studies on 980 nm diode laser vaporisation indicate high haemostatic potential, although anticoagulants or platelet aggregation inhibitors were taken in 24% and 52% of patients, respectively [505, 506]. In a number of studies, a high rate of post-operative dysuria was reported [503, 505-507].

Early publications on diode vaporisation reported high re-operation rates (8-33%) and persisting SUI (9.1%) [503, 505-507].

Practical considerations: Diode laser vaporisation leads to similar improvements in clinical and symptomatic parameters during short-term follow-up and provides good haemostatic properties. Based on the limited number of mainly low quality RCTs, and controversial data on the retreatment rate, results for diode laser vaporisation should be evaluated in further higher quality RCTs.

Summary of evidence	**LE**
Laser vaporisation of the prostate using the 120-W 980 nm diode laser demonstrated high intra-operative safety with regard to haemostatic properties when compared to TURP. Peri-operative parameters like catheterisation time and hospital stay were in favour of diode lasers. Evidence is limited by the number and quality of the available studies.	1b
In a number of studies, post-operative complications such as severe storage symptoms and persisting incontinence, occurred with laser vaporisation of the prostate using the 120-W 980 nm diode laser.	3
Laser vaporisation using the 120-W 980 nm diode laser seems to be safe with regard to haemostasis in patients receiving anticoagulant therapy.	3

*5.3.4 **Alternative ablative techniques***

5.3.4.1 Aquablation – image guided robotic waterjet ablation: AquaBeam

Mechanism of action: AquaBeam uses the principle of hydro-dissection to ablate prostatic parenchyma while sparing collagenous structures like blood vessels and the surgical capsule. A targeted high velocity saline stream ablates prostatic tissue without the generation of thermal energy under real-time transrectal ultrasound guidance. After completion of ablation haemostasis is performed with a Foley balloon catheter on light traction or diathermy or low-powered laser if necessary [508].

Efficacy: In a double-blind, multicentre, pivotal RCT, 181 patients with a prostate size of 30-80mL were randomised to TURP or Aquablation [509, 510]. Mean total operative time was similar for Aquablation and TURP (33 vs. 36 minutes), but resection time was significantly lower for Aquablation (4 vs. 27 minutes). At six months patients treated with Aquablation and TURP experienced large IPSS improvements (-16.9 and -15.1, respectively), satisfying the non-inferiority hypothesis. At one year follow-up, mean IPSS reduction was 15.1 with a mean reduction in IPSS score of 67% for both groups. No significant difference in improvement of IPSS, QoL, Q_{max} and reduction of PVR was reported between the groups [511].

Improvements in IPSS and Q_{max} were maintained after five years in both groups [512]. Mean IPSS decrease were 16.9 and 15.1 points in the Aquablation and TURP groups, respectively. Similarly, 5-year improvements in Q_{max} were 125% and 89% compared to baseline for Aquablation and TURP, respectively. Over five years, surgical retreatments were 5.1% and 1.5% respectively [512].

Results of AquaBeam in patients with large prostates (80-150mL) were evaluated in a cohort study of 101 men (WATER II) [509]. After twelve months, significant improvements were seen in IPSS (mean decrease of 17 points), Q_{max} (increase of 12.5 cc/sec) and PVR (a drop of 171 cc in those with PVR > 100 at baseline). At 5-years follow-up, 3% of patients required surgical retreatment [513].
Urodynamic studies of 66 patients enrolled in the WATER trial at six months follow-up showed significant changes in $p_{det}Q_{max}$ (reductions of 35 and 34 cm H20, respectively) and large improvements in BOO index in both groups [514].

Tolerability and safety: Results for the WATER trial have shown comparable hospital stay and catheterisation duration (1.4 and 1 day, respectively) [509]. One case of blood transfusion was reported after Aquabeam and none after TURP. In a SR of seven patient groups involving 446 patients treated by aquablation, although there was a significant haemoglobin drop (2.06 g/dL), it did not translate into increased transfusion rates. In WATER, fewer men in the Aquablation group had a persistent Clavien-Dindo grade 1 or 2 or higher adverse event compared to TURP (26% vs. 42%) at three months. Among sexually active men the rate of anejaculation was lower in those treated with Aquablation compared to TURP (10% vs. 36%, respectively). There were no procedure-related adverse events after six months [511].

In patients with a prostate volume between 80-150 mL (WATERII trial), bleeding related events were observed in fourteen patients (13.9%) of which eight (7.9%) occurred prior to discharge and six (5.9%) occurred within one month of discharge. Blood transfusions were required in eight patients, return to the theatre for fulguration in three patients, and both transfusion and fulguration in two patients [515]. Maintenance of antegrade ejaculation was slightly lower in WATER II at 81% compared to 90% in the smaller prostates of WATER I [516]. In WATER II there was a 2% *de novo* incontinence rate at twelve months [517].

In an analysis of procedural differences including data from WATER I and II, compared to a single pass of ablation, the use of two or more passes during Aquablation resulted in lower IPSS scores by four points, and lower IPSS QoL scores by 0.7 points at 24 and 36 months. Similarly, 36-month Q_{max} values were higher by 5 ml/sec in those with two or more passes than in those with one pass [518].

Practical considerations: During long-term follow-up, aquablation provides non-inferior functional outcomes compared to TURP in patients with LUTS and a prostate volume between 30-80 mL. Additional longer term, higher quality follow-up is necessary to assess better the clinical value of aquablation. There are still concerns about management of bleeding and bladder neck cautery is often performed at the end of the procedure.

Summary of evidence	**LE**
Aquablation appears to be as effective as TURP both subjectively and objectively.	1b

Recommendations	**Strength rating**
Offer Aquablation* to patients with moderate-to-severe LUTS and a prostate volume of 30-80 mL as an alternative to transurethral resection of the prostate.	Weak
Inform patients about the risk of bleeding and the lack of long-term follow-up data.	Strong

** Aquablation remains under investigation as evidence levels as described by Speakman et al. [317] has not been reached.*

5.3.4.2 Prostatic artery embolisation

Mechanism of action: Prostatic artery embolisation (PAE) can be performed as a day procedure under local anaesthesia with access through the femoral or radial arteries. Digital subtraction angiography displays arterial anatomy, and the appropriate prostatic arterial supply is selectively embolised to effect stasis in treated prostatic vessels. Different technical variations (including bead size) have been described for PAE, which needs specific training [519, 520].

Efficacy: Superior efficacy of PAE compared with a sham procedure was found in a six-month randomised, single-blind, sham-controlled trial in 80 patients with LUTS, refractory to medical treatment. The decrease in IPSS at six months was 5.03 +/- 8.13 in the sham group and 17.1 +/- 7.25 in the PAE group [521].

A SR and meta-analysis including RCTs and two non-RCTs comparative studies (n = 708 patients) showed that TURP achieved a significantly higher mean post-operative difference for IPSS and IPSS-QoL, 3.80 and 0.73 points, respectively compared to PAE [522]. All of the functional outcomes assessed were significantly superior after TURP: 3.62 mL/s for Q_{max}, 11.51 mL for prostate volume, 11.86 mL for PVR, and 1.02 ng/mL for PSA [522].

According to a Cochrane network meta-analysis, PAE may result in little to no difference in urologic symptoms scores as well as QoL compared to TURP at short-term follow-up of three to twelve months [523]. A network meta-analysis included outcome data at three to six months follow-up and concluded that improvement of IPSS was similarly high after TURP and PUL.

A meta-analysis of eleven RCTs comparing TURP and PAE found no significant difference between TURP and PAE for patient-reported outcomes including IPSS and QoL at twelve months. PAE was less effective regarding improvements in most functional outcomes such as maximum flow rate, prostate volume, and prostate-specific antigen [524].

A Cochrane review reported that compared to TURP, the impact on urological symptoms and QoL improvement as perceived by patients appears to be similar following PAE [525]. This review did reveal major uncertainty as to how major adverse events compare.

According to a non-inferiority trial, 21% of patients who initially had PAE underwent TURP within two years [526]

In a single-centre retrospective analysis of 75 PAE patients over a three-year period, PAE was shown to be a safe, effective, and durable treatment option for non-index patients with urinary retention (87% catheter free) or gross haematuria (resolved 87.5%) [527].

Tolerability and safety: Available RCTs, as well as SR and meta-analysis show conflicting results about the comparative rate of adverse events after PAE or TURP, depending on studies included, definition of adverse events, and follow-up. In a SR of comparative studies PAE resulted in significantly more adverse events than TURP/OP (41.6% vs. 30.4%). The frequency of AUR after the procedures was significantly higher in the PAE group (9.4% vs. 2.0%) [528]. In another compilation of studies, PAE was associated with significantly fewer overall adverse events but similar rates of severe side effects, as well as and shorter hospitalisation times (mean difference = -1.94 days), but longer procedural times (mean difference = 51.43 min) [529].

Another SR and meta-analysis of four studies (506 patients) comparing PAE and TURP found no significant difference in the post-operative complication rate between TURP and PAE [530].

According to a Cochrane network meta-analysis, PAE may also result in a large reduction in major adverse events than TURP, but the confidence interval includes substantial benefits and harms [523]. In addition, uncertainty exists about the effect of PAE on retreatment compared to TURP at follow-up from 12 to 60 months.

A meta-analysis did reveal major uncertainty as to how major adverse events compare between TURP and PAE [525].

Concerning sexual adverse events, the mean differences in IIEF-5 score were not significantly different between TURP and PAE in a meta-analysis [529]. Another meta-analysis of two RCTs detected no difference in retrograde ejaculation rates [415]. Post-operative erectile function measured by IIEF-5 was in favour of PAE with mean difference in change of 2.56 points. In another updated meta-analysis PAE was consistently associated with lower sexual dysfunction than TURP (OR 0.24) [531]. According to a Cochrane network meta-analysis, uncertainty exists on the effect of PAE on erectile function and ejaculatory function as compared to TURP [523].

Concerns still exist about non-target embolisation, reported in earlier studies [532]; however, more recent studies report less incidents [522, 533]. A SR of 22 studies reporting radiation exposure during PAE, with a twenty-fold range of exposures, estimated that the median risk for a 66-year-old patient of a cancer related death was 0.117%, equivalent to a reduced life expectancy of 5.4 days. Radiation exposure therefore should be part of the counselling for patients considered for PAE. These data suggest there is potential for significant radiation reduction in some centres using appropriate protocols [534].

Practical considerations: A multidisciplinary team approach of urologists and radiologists is mandatory and patient selection should be done by urologists and interventional radiologists. The investigation of patients with LUTS to indicate suitability for invasive techniques should be performed by urologists only. This technically demanding procedure should only be done by an interventional radiologist with specific mentored training and expertise in PAE [535]. There are data suggesting that larger prostates have a higher chance of a superior outcome with PAE in post hoc analysis of RCTs, but larger trials are required to clarify the most suitable patients for PAE [515, 536].

Further data with medium- and long-term follow-up are still required and comparison with other minimally invasive techniques would be valuable. However, current evidence of safety and efficacy of PAE appears adequate to support the use of this procedure for men with moderate-to-severe LUTS provided proper arrangements for consent and audit are in place; therefore, a recommendation has been given, but PAE remains under investigation.

Summary of evidence	**LE**
Prostatic artery embolisation is less effective than TURP at improving symptoms and urodynamic parameters such as flow rate.	1a
Procedural time is longer for PAE compared to TURP, but blood loss, catheterisation and hospitalisation time are in favour of PAE.	1b

Recommendations	Strength rating
Offer prostatic artery embolisation (PAE)* to men with moderate-to-severe LUTS who wish to consider minimally invasive treatment options and accept less optimal outcomes compared with transurethral resection of the prostate.	Weak
Perform PAE only in units where the work up and follow-up is performed by urologists working collaboratively with trained interventional radiologists for the identification of PAE suitable patients.	Strong

** PAE remains under investigation*

5.3.4.3 Alternative ablative techniques under investigation

5.3.4.3.1 Convective water vapour energy (WAVE) ablation: The Rezum system

Mechanism of action: The Rezum system uses radiofrequency power to create thermal energy in the form of water vapour, which in turn deposits the stored thermal energy when the steam phase shifts to the liquid phase upon cell contact. The steam disperses through the tissue interstices and releases stored thermal energy onto prostatic tissue effecting cell necrosis. The procedure can be performed in an office-based setting. Usually, one to three injections are needed for each lateral lobe and one to two injections may be delivered into the median lobe (depending on the prostate size).

Efficacy: In a multicentre RCT, 197 men were enrolled and randomised in a 2:1 ratio to treatment with water vapour energy ablation or sham treatment [537]. At three months relief of symptoms, (measured by a change in IPSS and Q_{max}) were significantly improved and maintained after WAVE therapy compared to the sham arm, although only the active treatment arm was followed up to twelve months. No relevant impact was observed on PVR. Quality of life outcome was significantly improved with a meaningful treatment response of 52% at twelve months. Further validated objective outcome measures such as BPH impact index (BPHII), Overactive Bladder Questionnaire Short Form for OAB bother, and impact on QoL and ICS Male Item Short Form Survey for male incontinence demonstrated improvements of symptoms at three months follow-up with sustained efficacy throughout the study period of twelve months. The reported two-year results in the Rezum cohort arm of the same study and the recently reported five-year results confirmed durability of the clinical outcome after convective water vapour energy ablation [538]. Surgical retreatment rate was 4.4% over five year. A Cochrane review found no studies comparing convective radiofrequency water vapour thermal therapy to any other active treatment form, such as TURP [539]. Another network meta-analysis included outcome data at three to six months follow-up and concluded that improvement of IPSS was similarly high after TURP and WAVE [540]. Objective outcomes (PVR and Q_{max}) were improved to the greatest extent after TURP, with moderate improvement after WAVE.

Tolerability and safety: Safety profile was favourable with adverse events documented to be mild-to-moderate and resolving rapidly. Preservation of erectile and ejaculatory function after convective water vapour thermal therapy was demonstrated utilising validated outcome instruments such as IIEF and Male Sexual Health Questionnaire-Ejaculation Disorder Questionnaire [537].

Practical considerations: There are two SRs of the Rezum cohort studies. One concludes that Rezum provides improvement in BPH symptoms that exceeds established minimal clinically important difference thresholds, preserves sexual function, and is associated with low surgical retreatment rates over four years. Therefore, suggesting that it may be a valuable addition to the urological armamentarium to treat LUTS in men with BPH [541]. The other, a Cochrane review reported that the certainty of evidence ranged from moderate to very low, with study limitations and imprecision being the most common reasons for down-grading of the evidence [539]. A Cochrane network meta-analysis reported uncertainty about the effects of Rezum on retreatment compared to sham treatment at three months follow-up and the certainty of evidence is very low [523]. Randomised controlled trials against a reference technique are needed to confirm the first promising clinical results and to evaluate mid- and long-term efficacy and safety of water vapour energy treatment.

5.3.5 ***Non-ablative techniques***

5.3.5.1 Prostatic urethral lift

Mechanism of action: Prostatic urethral lift (PUL) is a minimally invasive approach under local or general anaesthesia. Encroaching lateral lobes are compressed by small permanent suture-based implants delivered under cystoscopic guidance resulting in an opening of the prostatic urethra leaving a continuous anterior channel through the prostatic fossa.

Efficacy: Several reports have shown that PUL achieves a significant improvement in IPSS (-39% to -52%), Q_{max} (+32% to +59%) and QoL (-48% to -53%) [542-547]. In a meta-analysis of retrospective and prospective trials, pooled estimates showed an overall improvement following PUL, including IPSS, Q_{max}, and QoL [547]. A Cochrane review of the sham RCT and the RCT against TURP concluded that PUL appears less effective than TURP in improving urological symptoms (IPSS, Q_{max}) in both short- and long term, while QoL outcomes may be similar [548]. Prostatic urethral lift was evaluated vs. sham in a multicentre study with one [544] three [549] and five [550] years follow-up of the treated cohort. Improvements in IPSS, QoL, and Q_{max} were durable with improvement rates of 36%, 50%, and 44% at 60-month follow-up, respectively [550]. A network meta-analysis included outcome data at three to six months follow-up and concluded that improvement of IPSS was similarly high after TURP and PUL. Objective outcomes (PVR and Q_{max}) were improved to the greatest extent after TURP, with less improvement after PUL [540].

A retrospective observational study of 1,413 consecutive patients from North America and Australia split patients into those still voiding (Group A) and those in retention (Group B). The results from Group A were comparable to the results from the clinical trials and of the 165 patients in Group B 69% were catheter free after five days, 83% after one month and 89% by study end [551].

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%) [544, 547, 549, 550]. Most symptoms were mild-to-moderate in severity and resolved within two to four weeks after the procedure. In an RCT comparing PUL to TURP, surgical recovery was measured using a validated instrument. They found that recovery from PUL is more rapid and more extensive in the first three to six months [552]. A SR and meta-analysis found that sexual function with regard to erectile and ejaculatory function remained stable or improved slightly during the 24-month follow-up [547, 548, 553].
In an RCT comparing PUL to TURP, PUL resulted in superior quality of recovery and ejaculatory function preservation. Ejaculatory function and bother scores did not change significantly in either treatment arm [552].

A SR of surgical re-interventions of eleven studies (2,016 patients), among which TURP/laser (51%), repeat PUL (32.7%) and device explant (19.6%) were most common, revealed an annual rate of surgical re-intervention of 6% per year (95% CI: 3.0-8.9) [554]. The re-treatment rate was 13.6% over five years in a multicentre study comparing PUL vs. sham [550].

Practical considerations: There are only limited data on treating patients with an obstructed/protruding middle lobe [555]. The effectiveness in large prostate glands has not been shown yet. Long-term studies are needed to evaluate the duration of the effect in comparison to other techniques.

Summary of evidence	**LE**
Prostatic urethral lift improves IPSS, Q_{max} and QoL; these improvements are inferior to TURP at 24 months.	1b
Prostatic urethral lift has a low incidence of sexual side effects.	1b
Patients should be informed that long-term effects, including the risk of retreatment, have not been evaluated.	4

Recommendation	**Strength rating**
Offer Prostatic urethral lift (Urolift®) to men with LUTS interested in preserving ejaculatory function, with prostates < 70 mL and no middle lobe.	Strong

5.3.5.2 Intra-prostatic injections
Mechanism of action: Various substances have been injected directly into the prostate in order to improve LUTS including Botulinum toxin-A (BoNT-A), fexapotide triflutate (NX-1207) and PRX302. The primary mechanism of action of BoNT-A is through the inhibition of neurotransmitter release from cholinergic neurons [556]. The mechanisms of action for the injectables NX-1207 and PRX302 are not completely understood, but experimental data suggest apoptosis-induced atrophy of the prostate with both drugs [556].

Efficacy: A SR and meta-analysis showed no differences in efficacy of BoNT-A compared with placebo and concluded that there is no evidence of clinical benefit in medical practice [557]. The positive results from Phase II-studies have not been confirmed in Phase III-trials for PRX302 [558, 559]. Fexapotide triflutate (NX-1207) was evaluated in two multicentre placebo controlled double-blind randomised parallel group trials including a total

of 995 patients with a mean follow-up of 3.6 years, IPSS change from baseline was significantly higher and AUR rate was significantly reduced in the treatment arm. The authors concluded that NX-1207 is an effective transrectal injectable for long-term treatment for LUTS and that treated patients have reduced need for further intervention [560].

Tolerability and Safety: A SR and meta-analysis showed low incidence rates of procedure-related adverse events [557]. Two multicentre placebo controlled double-blind randomised parallel group trials with long-term follow-up evaluating NX-1207 detected no significant safety differences between the study arms [560].

Practical considerations: Positive results for PRX 302 from Phase II-studies have not been confirmed in Phase III-trials yet. Nevertheless, an RCT evaluating transperineal intraprostatic BoNT-A injection vs. TURP concluded that IPSS significantly decreased in all patients, with a non-significant difference between the arms and that the BoNT-A injection significantly maintained erectile function compared to TURP at twelve months [561]. More high-quality evidence against reference techniques is needed.

Summary of evidence	**LE**
Results from clinical trials have shown no clinical benefits for BoNT-A compared to placebo for the management of LUTS due to BPO.	1a
Results from clinical trials have shown clinical benefits for NX-1207 compared to placebo for the management of LUTS due to BPO.	1b

Recommendation	**Strength rating**
Do not offer intraprostatic Botulinum toxin-A injection treatment to patients with male LUTS.	Strong

5.3.5.3 Non-ablative techniques under investigation

5.3.5.3.1 (i)TIND

Mechanism of action: The iTIND is a nitinol device composed of three elongated struts and an anchoring leaflet. Under direct visualisation iTIND is deployed inside the prostate in expanded configuration. The intended mode of action is to compress obstructive tissue by the expanded device, thereby exerting radial force leading to ischaemic necrosis resulting in a Turner Warwick like incision. The iTIND device is left in position for five days and removed in an outpatient setting by standard urethroscopy.

Efficacy: A single-arm, prospective study of 32 patients with a three-year follow-up was conducted to evaluate feasibility and safety of the procedure [562]. The change from baseline in IPSS, QoL and Q_{max} was significant at every follow-up [563]. In a multicenter RCT, 175 men were randomised 2:1 between iTIND and sham procedures. Patients were assessed at baseline, 45 days, three, and twelve months postoperatively. A total of 78.6% of patients in the iTIND arm showed a reduction of ≥ 3 points in IPSS, vs. 60% of patients in the control arm at three months. At twelve months follow-up, the iTIND group reported a mean decrease of 9.25 in IPSS, of 1.9-point in QoL and a 3.52mL/s increase in Q_{max} compared to baseline [564]. In a prospective multicentre study, 81 patients were enrolled and treated with a second generation iTIND device. At twelve-month follow-up, mean IPSS decreased from 22.5 to 8.8 and Q_{max} at one month increased from 7.3 to 14.7 ml/s at twelve months [565].

Another network meta-analysis included outcome data at three to six months follow-up and concluded that IPSS improvement was lower after iTIND compared to TURP. Improvements in objective outcomes (PVR and Q_{max}) were also lower after iTIND [540].

Tolerability and safety: The device were reported as well tolerated by all patients. Four early complications (12.5%) were recorded, including one case of urinary retention (3.1%), one case of transient incontinence due to device displacement (3.1%), and two cases of infection (6.2%). No further complications were recorded during the 36-month follow-up period [563]. In the RCT against sham study adverse events were typically mild and transient, most were Clavien-Dindo grade 1 or 2 with 38.1% in the iTIND arm and 17.5% in the control arm [564]. No new ejaculatory or erectile dysfunction has been reported [564, 565].

In a prospective multicentre study, 81 patients were enrolled and treated with a second generation iTIND device. During the twelve-month period, two patients required medical therapy, two patients required TURP, and ten patients were lost to follow-up [565].

Practical considerations: Randomised controlled trials comparing iTIND to a reference technique are ongoing.

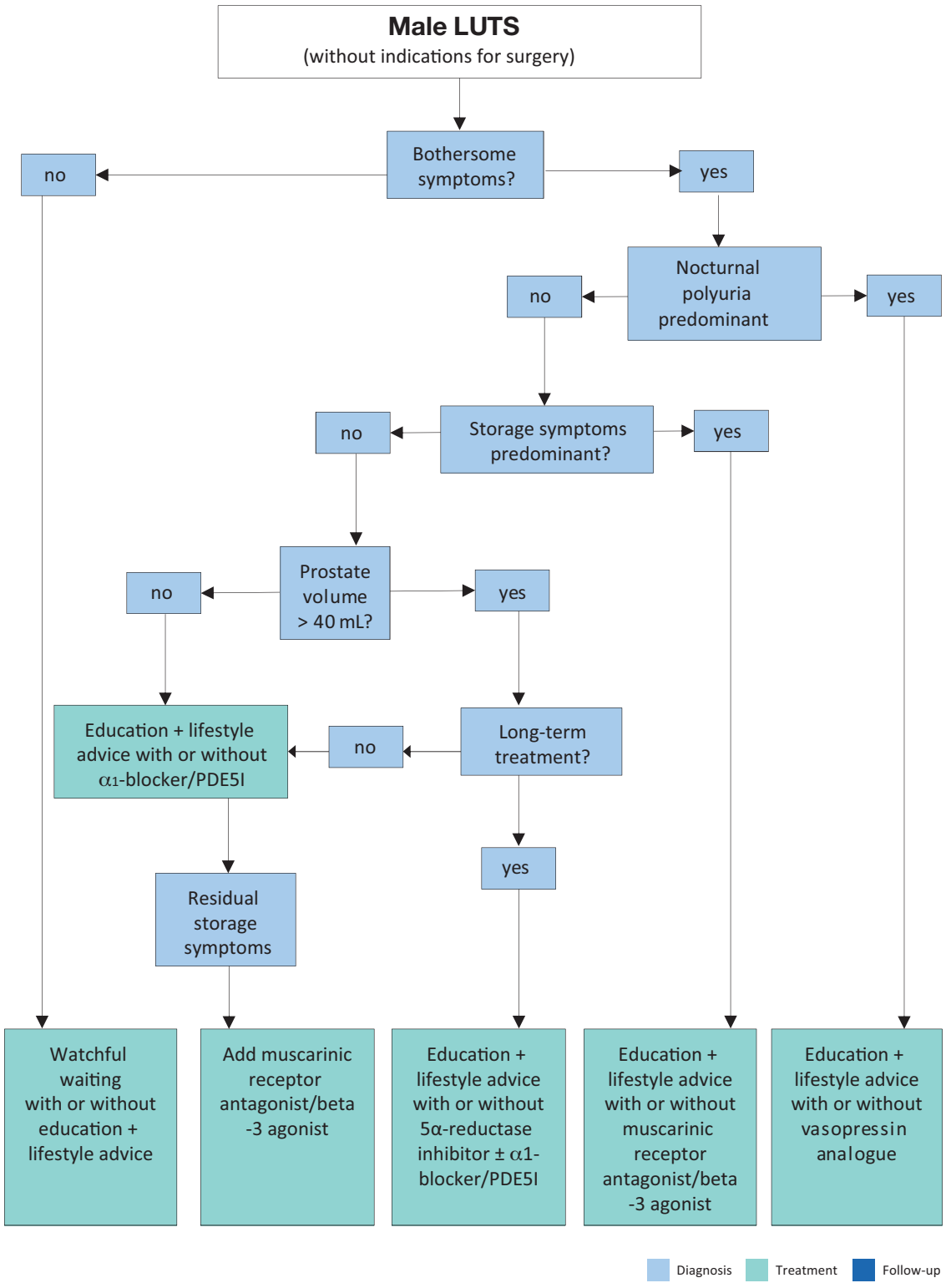
5.4 Patient selection for LUTS/BPO treatment

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.

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).

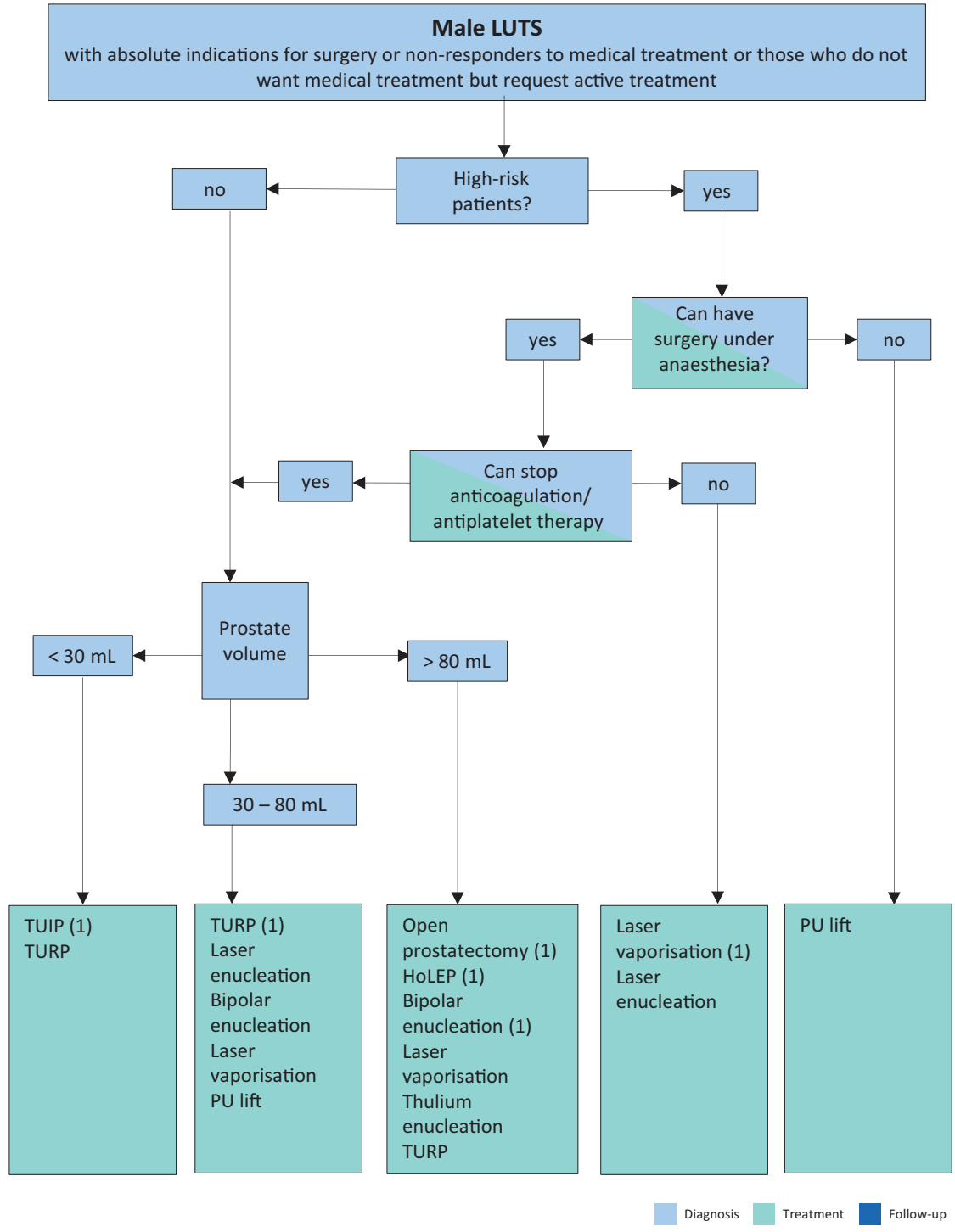
Additionally, surgery is usually needed when patients have not obtained adequate relief from LUTS or PVR using conservative or medical treatments (relative operation indications). The choice of surgical technique depends on prostate size, co-morbidities of the patient, ability to have anaesthesia, patients' 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.



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 is stratified by the patient's ability to have



(1) Current standard/first choice. The alternative treatments are presented in alphabetical order.
Laser vaporisation includes GreenLight, thulium, and diode laser vaporisation.
Laser enucleation includes holmium and thulium laser enucleation.
HoLEP = holmium laser enucleation; TUIP = transurethral incision of the prostate; TURP = transurethral resection of the prostate; PU = prostatic urethral.

5.5 Management of Nocturia in men with lower urinary tract symptoms

The following section reports a SR of therapy for the management of nocturia in men with LUTS. It also emphasises the need to consider the wide range of possible causes of nocturia [566].

Nocturia has been defined as the complaint of waking at night to void [3]. The ICS Standardisation Steering Committee has introduced the concept of *main sleep period,* defined as "the period from the time of falling asleep to the time of intending to rise for the next "day" [567].

Nocturia 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 2). 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 2: Categories of nocturia

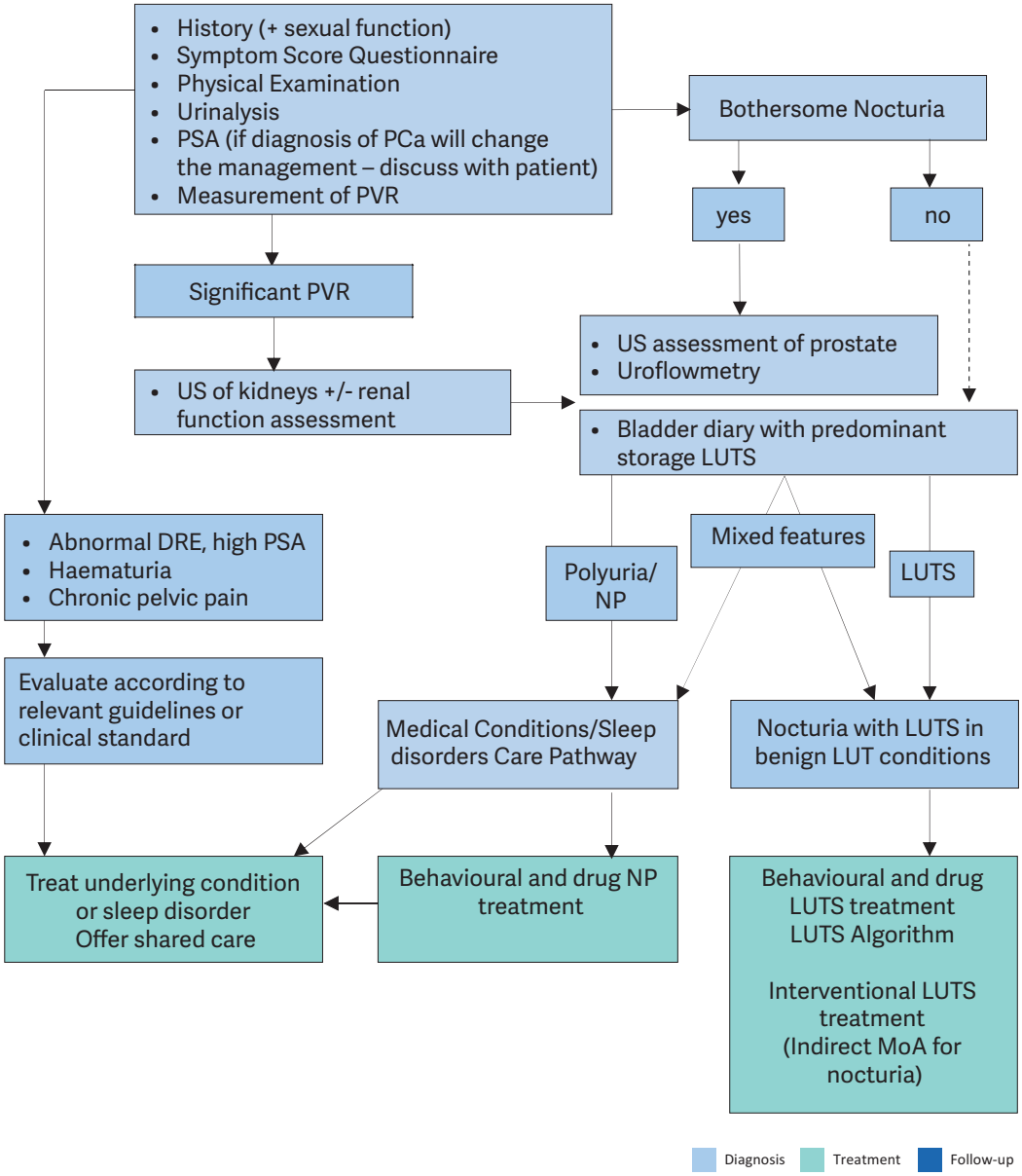
CATEGORY	Disproportionate urine production (at all times, or during sleep)	Low volume of each void (at all times, or overnight)
Behavioural	Inappropriate fluid intake	"Bladder awareness" due to secondary sleep disturbance
Systemic	Water, salt and metabolite output	
Sleep disorder	Variable water and salt 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, a sleep disorder or a combination. Therapy may be driven by the bother it causes, but non-bothersome nocturia may warrant assessment with a frequency volume chart (indicated by the dotted line) depending on history and clinical examination since potential presence of a serious underlying medical condition must be considered.
FVC = frequency volume chart; DRE = digital rectal examination; NP = nocturnal polyuria; MoA = mechanism of action; PVR = post-void residual; PSA = prostate-specific antigen; US = ultrasound.

*5.5.2 **Medical conditions and sleep disorders Shared Care Pathway***

Causative categories for nocturia comprise [568]:

1. bladder storage problems;
2. 24-hour polyuria (> 40 mL/kg urine output over a 24-hour period);
3. nocturnal polyuria (NP; defined as excessive production of urine during the individual's main sleep period, i.e. nocturnal output exceeding 20% of 24-hour urine output in the young, or 33% of urine output in people > 65 [3]);
4. sleep disorders;
5. mixed aetiology.

Potentially relevant systemic conditions are those which impair physiological fluid balance, including influences on the levels of free water, salt, other solutes, and plasma oncotic pressure; endocrine regulation e.g., by antidiuretic hormone; 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 (Table 3). 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, congestive cardiac failure, poorly controlled diabetes mellitus and medications (e.g., diuretics, or lithium).

Table 3: 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 • Increased exercise • Leg elevation • Weight loss Interventional therapy • Therapy of refractory storage LUTS • Therapy of refractory voiding LUTS	**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

ISC = intermittent self catheterisation

*5.5.3 **Treatment for Nocturia***

5.5.3.1 Antidiuretic therapy

The antidiuretic hormone arginine vasopressin (AVP) plays a key role in body water homeostasis and control of urine production by binding to V2 receptors in the renal collecting ducts. Arginine vasopressin increases water re-absorption and urinary osmolality, so decreasing water excretion and total urine volume. Arginine vasopressin also has V1 receptor mediated vasoconstrictive/hypertensive effects and a very short serum half-life, which makes the hormone unsuitable for treating nocturia/nocturnal polyuria.

Desmopressin is a synthetic analogue of AVP with high V2 receptor affinity and no relevant V1 receptor affinity. It has been investigated for treating nocturia [569], with specific doses, titrated dosing, differing formulations, and options for route of administration. Most studies have short follow-up. Global interpretation of existing studies is difficult due to the limitations, imprecision, heterogeneity and inconsistencies of the studies.

A SR of randomised or quasi-randomised trials in men with nocturia found that desmopressin may decrease the number of nocturnal voids by -0.46 compared to placebo over short-term follow-up (up to three months); over intermediate-term follow-up (three to twelve months) there was a change of -0.85 in nocturnal voids in a substantial number of participants without increase in major adverse events [570].

Another SR of comparative trials of men with nocturia as the primary presentation and LUTS including nocturia or nocturnal polyuria found that antidiuretic therapy using dose titration was more effective than placebo in relation to nocturnal voiding frequency and duration of undisturbed sleep [566]. Adverse events include headache, hyponatremia, insomnia, dry mouth, hypertension, abdominal pain, peripheral edema, and nausea. Three studies evaluating titrated-dose desmopressin in which men were included, reported seven serious adverse events in 530 patients (1.3%), with one death. There were seventeen cases of hyponatraemia (3.2%) and seven of hypertension (1.3%). Headache was reported in 53 (10%) and nausea in fifteen (2.8%) [566]. Hyponatremia is the most important concern, especially in patients > 65 years of age, with potential life-threatening consequences. Baseline values of sodium over 130 mmol/L have been used as inclusion criteria in some research protocols. Assessment of sodium levels must be undertaken at baseline, after initiation of treatment or dose titration and during treatment. Desmopressin is not recommended in high-risk groups [566].

Desmopressin oral disintegrating tablets (ODT) have been studied separately in the sex-specific pivotal trials CS41 and CS40 in patients with nocturia [571, 572]. Almost 87% of included patients had nocturnal polyuria and approximately 48% of the patients were > 65 years. The co-primary endpoints in both trials were change in number of nocturia episodes per night from baseline and at least a 33% decrease in the mean number of nocturnal voids from baseline during three months of treatment. The mean change in nocturia episodes from baseline was greater with desmopressin ODT compared to placebo (difference: women = -0.3 [95% CI: -0.5 to -0.1]; men = -0.4 [95% CI: -0.6 to -0.2]). The 33% responder rate was also greater with desmopressin ODT compared to placebo (women: 78% vs. 62%; men: 67% vs. 50%).

Analysis of three published placebo-controlled trials of desmopressin ODT for nocturia showed that clinically significant hyponatraemia was more frequent in patients aged ≥ 65 years than in those aged < 65 years in all dosage groups, including those receiving the minimum effective dose for desmopressin (11% of men aged ≥ 65 years vs. 0% of men aged < 65 years receiving 50 mcg; 4% of women ≥ 65 aged years vs. 2% of women aged < 65 years receiving 25 mcg). Severe hyponatraemia, defined as ≤ 125 mmol/L serum sodium, was rare, affecting 22 of 1,431 (2%) patients overall [573]. In a cases series including men aged of more than 60 treated with 50 mcg ODT, only 12/80 men had hyponatremia (non-severe) after one week. Hyponatraemia persistence was noted in 4/12 cases after reduction to 25 mcg [574].

Low-dose desmopressin ODT has been approved in Europe, Canada and Australia for the treatment of nocturia with ≥ 2 episodes in gender-specific low doses 50 mcg for men and 25 mcg for women; however, it initially failed to receive FDA approval, with the FDA citing uncertain benefit relative to risks as the reason. Following resubmission to the FDA in June 2018 desmopressin acetate sublingual tablet, 50 mcg for men and 25 mcg for women, was approved for the treatment of nocturia due to nocturnal polyuria in adults who awaken at least two times per night to void with a boxed warning for hyponatremia.

Desmopressin acetate nasal spray is a new low-dose formulation of desmopressin and differs from other types of desmopressin formulation due to its bioavailability and route of administration. Desmopressin acetate nasal spray has been investigated in two RCTs including men and women with nocturia (over two episodes per night) and a mean age of 66 years. The average benefit of treatment relative to placebo was statistically significant but low, -0.3 and -0.2 for the 1.5 mcg and 0.75 mcg doses of desmopressin acetate, respectively. The number of patients with a reduction of more than 50% of nocturia episodes was 48.5% and 37.9%, respectively compared with 30% in the placebo group [575]. The reported adverse event rate of the studies was rather low, and the risk of hyponatremia was 1.2% and 0.9% for desmopressin acetate 1.5 mcg and 0.75 mcg, respectively. Desmopressin acetate nasal spray was approved by the FDA in 2017 for the treatment of nocturia due to nocturnal polyuria, but it is not available in Europe.

Practical considerations: A complete medical assessment should be made, to exclude potentially non-urological underlying causes, e.g., sleep apnoea, before prescribing desmopressin in men with nocturia due to nocturnal polyuria. The optimal dose differs between patients, in men < 65 years 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. Desmopressin is taken once daily before sleeping. Patients should avoid drinking fluids at least one hour before and for eight hours after dosing. Low dose desmopressin may be prescribed in patients > 65 years. In men ≥ 65 years or older, low dose desmopressin should not be used if the serum sodium concentration is below normal: all patients should be monitored for hyponatraemia. Urologists

should be cautious when prescribing low-dose desmopressin in patients under-represented in trials (e.g., patients > 75 years) who may have an increased risk of hyponatraemia.

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. Applicable medications include; selective α1-adrenergic antagonists [576], antimuscarinics [577-579], 5-ARIs [580] and PDE5Is [581]. However, effect size of these medications is generally small, or not significantly different from placebo when used to treat nocturia [566]. Data on OAB medications (antimuscarinics, beta-3 agonist) generally had a female-predominant population. No studies specifically addressing the impact of OAB medications on nocturia in men were identified [566]. Benefits with combination therapies were not consistently observed.

5.5.3.3 Other medications

Agents to promote sleep [582], diuretics [583], non-steroidal anti-inflammatory agents (NSAIDs) [584] and phytotherapy [585] were reported as being associated with response or QoL improvement [566]. 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. One RCT has compared melatonin+tamsulosin compared to placebo+tamsulosin and found no difference on IPSS change [586]. Agents to promote sleep do not appear to reduce nocturnal voiding frequency but may help patients return to sleep.

Summary of evidence	**LE**
No clinical trial of pathophysiology-directed primary therapy has been undertaken.	4
No robust clinical trial of behavioural therapy as primary intervention has been undertaken.	4
Antidiuretic therapy reduces nocturnal voiding frequency in men with baseline severity of two or more voids per night.	1b
There is an increased risk of hyponatremia in patients 65 years of age or older under antidiuretic therapy.	1b
Antidiuretic therapy increases duration of undisturbed sleep.	1b
Alpha 1-blocker use is associated with improvements in undisturbed sleep duration and nocturnal voiding frequency, which are generally of only marginal clinical significance.	2
Antimuscarinic medications can reduce night-time urinary urgency severity, but the reduction in overall nocturia frequency is small or non-significant.	2
Antimuscarinic medications are associated with higher incidence of dry mouth compared with placebo.	2
5α-reductase inhibitors reduce nocturia severity in men with baseline nocturia severity of two or more voids per night.	2
A trial of timed diuretic therapy may be offered to men with nocturia due to nocturnal polyuria. Screening for hyponatraemia should be undertaken at baseline and during treatment.	1b

Recommendations	**Strength rating**
Treat underlying causes of nocturia, including behavioural, systemic condition(s), sleep disorders, lower urinary tract dysfunction, or a combination of factors.	Weak
Discuss behavioural changes with the patient to reduce nocturnal urine volume and episodes of nocturia and improve sleep quality.	Weak
Offer desmopressin to decrease nocturia due to nocturnal polyuria in men < 65 years of age.	Weak
Offer low dose desmopressin for men > 65 years of age with nocturia at least twice per night due to nocturnal polyuria.	Weak
Screen for hyponatraemia at baseline, day three and day seven, one month after initiating therapy and periodically during treatment. Measure serum sodium more frequently in patients > 65 years of age and in patients at increased risk of hyponatraemia.	Strong
Discuss with the patient the potential clinical benefit relative to the associated risks from the use of desmopressin, especially in men > 65 years of age.	Strong
Offer α1-adrenergic antagonists for treating nocturia in men who have nocturia associated with LUTS.	Weak

Offer antimuscarinic drugs for treating nocturia in men who have nocturia associated with overactive bladder.	Weak
Offer 5α-reductase inhibitors for treating nocturia in men who have nocturia associated with LUTS and an enlarged prostate (> 40 mL).	Weak
Do not offer phosphodiesterase type 5 inhibitors for the treatment of nocturia.	Weak

5.6 Management of male urinary incontinence

The aim of the following section is to provide evidence-based recommendations for the management of male UI.

5.6.1 Epidemiology and Pathophysiology

Urinary incontinence is defined as an unintentional loss of urine and is reported to have a prevalence of 11% in men aged 60 to 64 years old to 31% in men ≥ 85 years and to affect up to 32% of men with LUTS [587-589]. Urinary incontinence can be further classified into three types: SUI, UUI and mixed urinary incontinence (MUI). Overflow UI, post-micturition dribble, nocturnal enuresis, and total incontinence are specific forms of UI that are outside the current scope of this guideline. An overview of the epidemiology and pathophysiology of male UI is given in table 4.

Table 4: Epidemiology and pathophysiology overview of male UI [589-593].

Type	Definition	Causes and associated factors	Pathophysiology	Clinical presentation
Stress UI: prevalence < 10%	Urine loss during movement, on effort or in general during increased abdominal pressure.	• Benign Prostatic Obstruction surgery • Neurogenic condition • Pelvic surgery • Radical prostatectomy • Urethral surgery	Sphincter deficiency	**Symptoms:** UI during physical activity, exercises, e.g. during coughing, sneezing,no leakage during sleep, no nocturnal enuresis **Voiding diary/Pad test:** with activity **Cough stress test:** leakage can coincide with coughing
Urgency UI: prevalence 40-80%	Urine loss concomitant or immediately following an urgency episode.	• Ageing process • Anorectal dysfunction/GI disorders • Behavioural factors (fluid intake and caffeine consumption) • BPO • Idiopathic • Intrinsic bladder diseases (cystitis, fibrosis, interstitial cystitis) • Metabolic syndrome [594] • Neurogenic conditions • UTIs	• Detrusor overactivity (neurogenic or not) • Urothelial stimulation • Increased afferent signalling • Others (pelvic organ cross talk, bladder wall ischemia etc.)	**Symptoms:** usually associated with, increased frequency and nocturia **Voiding diary:** urgency, frequency and nocturia, incontinence

Mixed UI: prevalence 10-30%	Any combination of SUI and UUI.	Causes of both SIU and UUI	Combination of SUI and UUI	**Symptoms:** UI on effort and with a sense of urgency **Voiding diary:** variable **Cough stress test:** may show leakage with coughing

BPO = benign prostatic obstruction; GI = gastrointestinal; SUI = stress urinary incontinence; UI = urinary incontinence; UTI = urinary tract infection; UUI = urgency urinary incontinence

*5.6.2 **Diagnostic Evaluation***

Medical history and physical examination of males with UI is the same as for male LUTS (Figure 2) and should allow UI to be categorised into SUI, UUI or MUI and to identify other types of UI (overflow UI, nocturnal enuresis), or those who need rapid referral to an appropriate specialist (e.g. pelvic diseases, neurological conditions).

Specific validated questionnaires, such as the ICIQ-UI-SF, can help to quantify UI severity; however, a detailed description of the different urinary symptoms questionnaires and PROMs is beyond the scope of this guideline. For more information on available questionnaires see the 7th International Consultation on Incontinence (ICI) review on patient reported outcomes assessment [595].

Voiding diaries are a standardised method of measuring symptom severity, including frequency and extent of UI episodes, voided volume and 24-hour or nocturnal total urine volume [43].

Pad tests can be used to quantify severity of UI and to monitor patient's response to treatment although the usefulness of these tests in differentiating between the different types of incontinence or predicting outcome of treatment is uncertain. Despite this, early post-operative testing with pad tests may predict future continence in men after radical prostatectomy [596, 597].

Urodynamic testing

Urodynamic studies allows for an objective characterisation of the type of UI and the identification of additional storage and/or voiding dysfunctions [598]

UDS in patients with UI following BPO surgery

Sphincter weakness is the most common finding in incontinent men after BPO surgery. However, data coming mostly from case series and reviews, show that besides sphincter incompetence, other LUTD, assessed via UDS, play an incident role in post BPO surgery incontinence.

Urodynamics has been performed in a retrospective study on 125 patients with incontinence after surgery for BPO. Sphincter insufficiency was the most common finding. However, also decreased detrusor compliance and DO have emerged as a cause of incontinence on urodynamic examination. Interestingly, both impaired detrusor contraction and DO alone were responsible for UI in 4 to 14% of patients [599].

UDS in patients with UI following radical prostatectomy

Also in this case, UI, is mainly due to sphincter deficiency. However, a SR on urodynamic findings in UI patients following radical prostatectomy, showed that while intrinsic urethral sphincter deficiency was reported as the sole cause of UI following radical prostatectomy in 8-71% of cases, it was variably associated with detrusor dysfunction in 0–88% of cases. In details, sphincter weakness was associated with DO in 0–100% of patients, with reduced bladder compliance in 18-58%, and with both DO and reduced bladder compliance in 4-64%. Interestingly, incontinent patients who did not complain of sphincter impairment showed detrusor dysfunction as follows: DO in 0-4%, reduced bladder compliance in 1-12%, DO plus impairment of bladder compliance in 1-7% [600].

UDS in patients with storage symptoms

In a retrospective evaluation of 668 urodynamic studies involving men with symptoms of urgency with or without urgency UI, DO was documented in 258 patients (38.6%) and 293 patients (43.9%) had evidence of BOO during PFS. The symptom UI correlated with the presence of DO [601].

The aforementioned evidence emphasises how urodynamic examination serves to clarify the origin of incontinence and the presence of any other associated LUTS. Unfortunately, the level of the evidence for the impact of UDS in the evaluation/management/outcome prediction of male patients with UI remains low [602] and does not allow us to produce any recommendations.

Therefore, UDS should be considered in selected patients with UI or persistent/*de novo* LUTS/UI after surgery, mainly when invasive treatments are considered [603].

Post-void residual volume measurement can be applied with caution to men with non-neurogenic UI, as the prevalence, severity, and clinical application of PVR in men with UI is uncertain. However, a post-void residual measurement helps to distinguish overflow incontinence from other UI types [604].

Urethrocystoscopy can be performed in selected patients to exclude urethral or bladder neck strictures. Some tests have been proposed to evaluate any sphincter function e.g., repositioning tests but with poor reliability. The examination of the bladder helps to exclude tumours, stones, diverticula, that may exacerbate UI [605].

Imaging (US, MRI, CT scan) can improve the understanding of the anatomical and functional abnormalities that may cause UI and thus help its management [606].

Urinalysis: Reagent strip ('dipstick') urinalysis may indicate UTI, proteinuria, haematuria, or glycosuria, requiring further tests as recommended according to other EAU Guidelines, e.g., Guidelines on urinary tract cancers and urological infections [48-51].

Summary of evidence	**LE**
Validated specific symptom score questionnaires and voiding diaries assist in the screening for and categorisation of UI.	3
Pad test can be used to quantify the presence and severity of UI, as well as a patient's response to treatment.	3
There is limited evidence that urodynamics and PVR affect treatment choice in men with uncomplicated UI.	3

Recommendation	**Strength rating**
Take a complete medical history including symptoms and co-morbidities, medications, and a focused physical examination in the evaluation of men with urinary incontinence (UI).	Strong
Use a validated symptom score questionnaire, bladder diary and pad-test to assess UI.	Strong
Measure post-void residual in the assessment of UI.	Strong
Perform urodynamics for UI when considering invasive treatment.	Weak

*5.6.3 **Conservative treatment***

5.6.3.1 Simple clinical interventions

5.6.3.1.1 Lifestyle interventions

Examples of lifestyle factors that may be associated with UI include obesity, smoking, level of physical activity and diet. Modification of these factors may improve UI, but most of the evidence for these interventions come from studies with predominately female study populations. However, as many of these interventions are now generalised public health measures their recommendation is in line with general medical practice [607-609]. Current evidence does not allow to adequately personalise lifestyle interventions according to the type of UI.

Modification of fluid intake, particularly restriction, is a strategy commonly used by people with UI to relieve symptoms. Advice on fluid intake given by healthcare professionals should be based on 24-hour fluid intake and urine output measurements. From a general health point of view, it should be advised that fluid intake should be sufficient to avoid thirst and that low or high 24-hour urine output should be investigated [607, 610, 611]. A cross-sectional population survey found no statistical association between caffeine intake and UI [612]. Conversely, an RCT showed that reduction of caffeine intake, associated with behavioural therapy, resulted in reduced urgency but not UI compared to behavioural therapy alone [613].

5.6.3.1.2 Treatment of co-morbidities

Urinary incontinence, especially in the elderly, has been associated with multiple co-morbid conditions [614]. It is possible that improvement of associated disease may reduce the severity of urinary symptoms. However, this is often difficult to assess as patients frequently suffer from more than one condition. Interventions may be combined and individualised, making it impossible to decide which alteration in an underlying disease has affected a patient's UI.

In patients with existing UI, particularly the elderly, it may be difficult or impossible to distinguish between the effects of medication, co-morbidities or ageing on UI. Although changing drug regimens for underlying diseases may be considered as a possible early intervention, there is limited evidence of benefit [615]. There is also a risk that stopping or altering medication may result in greater harm than benefit.

5.6.3.1.3 Constipation

One RCT, with a majority female population, 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 [616]. However, there is no evidence to show whether treating constipation improves UI, although both constipation and UI appear to be improved by certain behavioural interventions.

5.6.3.1.4 Containment

Containment includes the use of absorbent pads, urinary catheters, external collection devices and penile clamps. A SR of six RCTs comparing different types of pads found that pads filled with super absorbent material were better than standard pads [617]. For men with light UI, a randomised crossover trial found that a leaf-shaped type of pad was preferred to rectangular pads [618].

A Cochrane review compared different types of long-term indwelling catheters and found no evidence that one catheter material or type of catheter was superior to another [619]. A SR of non-randomised studies found no differences in UTI outcome or Upper Urinary Tract (UUT) changes between use of suprapubic or urethral catheter drainage; however, patients with suprapubic catheters were less likely to have urethral complications [620]. For people using intermittent catheterisation, a Cochrane review found no evidence that one type of catheter or regimen of catheterisation was better than another [621].

An RCT in 56 men with post-prostatectomy incontinence (PPI) compared sheath drainage system, body-worn urinal, penile clamp, and absorbent pads. It was found that the three devices and absorbent pads have different strengths and limitations that make them more (or less) suitable for particular activities. Most men prefer to use a combination of devices and pads to meet their lifestyle needs. Hinge-type penile clamp was good for short vigorous activities as it was the most secure, least likely to leak and most discreet, although almost all men described it as uncomfortable or painful [622].

Summary of evidence	**LE**
There is limited evidence that lifestyle interventions e.g., weight reduction, smoking cessation or diet modification improves UI in males.	3
There is limited evidence that improving co-morbidities or changing drug regimens for underlying disease improves UI in males.	3
Pads and/or penile sheaths are palliative options for management of both SUI and UUI.	1b

Recommendations	**Strength rating**
Offer lifestyle advice that may improve urinary incontinence (UI) to patients; however, patients should be informed that the evidence for these interventions is lacking.	Weak
Review any medication associated with the development or worsening of UI.	Weak
Use pads and/or penile sheaths as a palliative option for the management of UI.	Weak

5.6.3.2 Behavioural and Physical therapies

Behavioural and physical therapies encompass all treatments which require a form of self-motivated personal retraining by the patient and include techniques that are used to augment this effect. Usually in clinical practice, these will be introduced as part of a package of care including lifestyle changes, patient education, and possibly cognitive therapy as well. Further details for behavioural treatments are outlined in section 5.1.2 of these guidelines.

5.6.3.2.1 Prompted or timed voiding

With prompted voiding, carers rather than the patient, initiate the decision to void. Two SRs confirmed a positive effect on continence outcomes for prompted voiding in comparison to standard care [623, 624]. 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, included two RCTs, found inconsistent improvement in continence compared with standard care in cognitively impaired adults [625].

5.6.3.2.2 Bladder training

Bladder training 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 program for UI is unclear. It is also unclear whether BT can prevent the development of UI. The addition of BT to anticholinergic therapy did not improve UI compared to antimuscarinics alone but it did improve frequency and nocturia [626]. In seven RCTs, BT was compared to drug therapy alone, and showed only a benefit for oxybutynin in cure and improvement of UI [626].

5.6.3.2.3 Pelvic floor muscle training

A 2015 Cochrane review concluded that there was no overall benefit at twelve months post-surgery for men who received post-operative pelvic floor muscle training (PFMT) for the treatment of PPI and that the benefits of conservative treatment of PPI remain uncertain [627]. However, a subsequent SR and meta-analysis showed that PFMT either alone or in combination with biofeedback and/or electrical stimulation was effective for treating PPI, significantly reducing the time to continence recovery [628]. A further meta-analysis demonstrated that the addition of guided programs using biofeedback and/or pelvic floor muscle electric stimulation (PFES) significantly improved continence recovery rates at one- and three-month intervals post-surgery compared to PFMT alone [629].

Pelvic floor muscle training as soon as possible after surgery (I.e., between seven and ten days after the withdrawal of the urethral catheter) [630].

An RCT demonstrated that even a single-session of pre-operative PFMT with biofeedback from a dedicated pelvic floor physiotherapist, has beneficial effects on post-prostatectomy UI in the short term after surgery and is effective in improving LUTS related QoL in the long term [631, 632]

Two subsequent SRs in patients who underwent robotic-assisted radical prostatectomy demonstrated that the addition of PFMT to the post-operative management plan shorten the time to continence recovery [633, 634].

Two RCTs have shown that written instructions alone offer similar levels of improvement to supervised PFMT [635, 636]. 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 [637].

One RCT compared PFMT to no treatment in men undergoing TURP. There was no demonstrable difference in the incidence of post-operative incontinence up to twelve months [638]. On the other hand, an RCT in men who underwent HoLEP, demonstrated that PFMT when started pre-operatively promoted early recovery of continence [639].

Other RCTs demonstrated that like PFMT, increased pelvic floor muscle strength and quicker return to continence may be achieved with the Pilates method [640], the oscillating rod [641], a combination of biofeedback with electrostimulation [642] and whole-body vibration training [643]. Furthermore, quicker return to continence and improved QoL may be achieved, even with extended and continuing nursing care [644]

5.6.3.2.4 Electrical stimulation

The majority of evidence on electrical stimulation refers to women with SUI and many are generally low quality, with a variety of stimulation parameters, treatment regimens and outcome parameters [638].

An RCT of 70 PPI men receiving surface or intra-anal electrostimulation reported a significant reduction in UI in terms of grams of urine loss and a significant improvement in QoL from baseline, but no statistically significant difference between treatment arms [645].

A Cochrane review of six RCTs on electrical stimulation in men with UI concluded that there was some evidence that electrical stimulation enhanced the effect of PFMT in the short-term but not after six months. Electrical stimulation was also more effective than sham stimulation at six, but not twelve months; however, there were more adverse effects including pain and discomfort with electrical stimulation [646].

Electromagnetic stimulation has been promoted as a treatment for UI, but only weak evidence of the short- and long-term effects has been reported in SRs [647, 648].

A more recent SR found insufficient evidence to suggest that electrical stimulation is beneficial for male patients with post-prostatectomy UI [649].

5.6.3.2.5 Posterior tibial nerve stimulation

Posterior tibial nerve stimulation (PTNS) has been studied as a treatment of UI, especially UUI. Electrical stimulation of the posterior tibial nerve delivers electrical stimuli to the sacral micturition centre via the S2-S4 sacral nerve plexus. Stimulation is done either percutaneously using a fine, 34-G, needle, inserted just above the medial aspect of the ankle (P-PTNS) or transcutaneously using surface electrodes (T-PTNS). Percutaneous-PTNS treatment cycles typically consist of twelve weekly treatments of 30 minutes and T-PTNS treatment cycles typically consists of self-administered, twenty-minute daily sessions, after adequate education.

A female-predominant sham controlled RCT, assessed the effectiveness of PTNS in OAB population. There were 22.8% and 20% males in the treatment and sham arms, respectively [650]. Overactive bladder symptoms improved significantly in 54.5% of patients in the PTNS arm compared to 20.9% in the sham arm. A non-inferiority RCT comparing T-PTNS compared to P-PTNS, reported significant improvements in daytime frequency, urgency and UUI episodes without significant difference between treatment arms after twelve weeks of therapy [651]. A SR on T-PTNS in idiopathic and neurogenic female-predominant (males < 10%) population, reported significant improvement in OAB symptoms in 48-93% of patients and cure of UUI episodes in 25-45% [652].

For PTNS, mild pain and discomfort at the puncture site is the most common adverse event [653]. Small haematomas, swelling, leg tingling and vasovagal reaction to needle placement have also been reported [650]. Treatment adherence is generally high at 89.7% [651]. Contra-indications include a cardiac pacemaker and skin disease at the site of stimulation.

There is some evidence that PTNS may benefit male patients with OAB, but due to too insufficient data, no recommendation on PTNS in males can be made at this time. However, considering the safety of this therapy, it can be offered to male patients as an alternative option prior to more invasive treatments.

Summary of evidence	**LE**
Prompted voiding, either alone or as part of a behavioural modification programme, improves continence in elderly, care-dependent people.	1b
The combination of bladder training with antimuscarinic drugs does not result in greater improvement of UI but may improve frequency and nocturia.	1b
There is conflicting evidence on whether the addition of BT, electrostimulation or biofeedback increases the effectiveness of PFMT alone.	1b
Pre-operative PFMT does not confer additional benefit to men undergoing radical prostatectomy.	1b
Electrical stimulation may add benefit to PFMT up to six months.	2
There is limited evidence for the effectiveness of PTNS in male population.	2
There is no evidence that PTNS cures UUI in male population.	2

Recommendations	**Strength rating**
Implement prompted voiding for patients with urinary incontinence (UI) where appropriate.	Strong
Offer bladder training as a complementary treatment for UI.	Weak
Offer pelvic floor muscle training alone or in combination with biofeedback and/or electrostimulation to men undergoing radical prostatectomy to speed recovery from UI.	Weak

5.6.4 ***Pharmacological management***

5.6.4.1 Drugs for urgency urinary incontinence

Muscarinic receptor antagonists [654-657] and beta-3 agonist [308-310, 658-661] are currently the first-line pharmacological treatments for UUI. The mechanism of action, efficacy, and safety and tolerability profiles of both classes of drugs are discussed in detail in sections 5.2.3 and 5.2.4, respectively.

5.6.4.2 Drugs for stress urinary incontinence

A SR of eight studies evaluating the efficacy of duloxetine in postprostatectomy SUI reported that duloxetine resulted in a mean dry rate of 58% (25–89%), mean improvement in pad number of 61% (12–100%), and mean improvement in one-hour pad weight of 68% (53–90%), at short-term follow-up (mean one to nine months) [662]. However, mean adverse event rates were high, and treatment was discontinued in 38% of cases. The most common adverse events included: fatigue, somnolence and nausea and were reported in 18% of patients [662]. The overall certainty of the evidence was low due to study heterogeneity and methodological limitations. Further RCTs with long-term follow-up are required. Duloxetine is currently prescribed in an off-label setting.

Summary of evidence	**LE**
Antimuscarinic monotherapy can significantly improve urgency, UUI, and increased daytime frequency.	1b
Mirabegron is superior to placebo and as efficacious as antimuscarinics for improvement of UUI.	1b
Duloxetine led to a short-term improvement in post-prostatectomy SUI symptoms and QoL improvement; however, a significant proportion of men discontinued treatment.	1b

Recommendations	**Strength rating**
Offer antimuscarinic drugs or mirabegron to adults with urgency urinary incontinence who failed conservative treatment.	Strong
Offer duloxetine to men with stress urinary incontinence.	Weak
Inform patients about the possible adverse events of duloxetine and that its use is off label for this indication in Europe.	Strong

5.6.5 ***Surgical treatment for stress urinary incontinence***

5.6.5.1 Bulking agents in men

Mechanism of Action: Urethral bulking agents work by adding bulk and improving the coaptation of a damaged sphincter zone. They represent a treatment option for men with either small volume leak or for those unfit for more invasive treatment options [663].

Efficacy: A Cochrane review on surgical treatment of PPI identified only one RCT that fulfilled the inclusion criteria. This trial randomised 45 men to Macroplastique injection or artificial urinary sphincter (AUS) implantation and compared their outcomes at 48 months [663]. Significant improvement was reported in both groups for men with minimal incontinence, but in men with total incontinence there was a significant difference in continence rates favouring AUS implantation (72% vs. 23%) [664]. A SR of eight studies (n=142) in men using Macroplastique, Opsys, Durasphere and Urolastic, showed short-term improvement, and reported dry rates between 0-83% [663]. A propensity score-matched analysis of 104 men with PPI, compared submucosal injection of Macroplastique to transobturator male sling (TiLOOP male) [665]. At twelve months follow-up, the reported failure free rates were 15.4% and 76.9%, the daily use of 0-1 pads was 21.2% and 67.3% and the satisfaction rate was 3.8% and 71.2%, respectively. Several small cohort studies of several different bulking agents have not shown any benefit.

A narrative review including data from 25 articles, reports a success rate with all bulking procedures of 54.3%, with 37.5% of symptoms improvement and almost 30% of dryness [666].

In a SR and meta-analysis, three studies addressed bulking agents. Two of them, involving a total of 384 participants, showed a pooled short-term cure rate of 26.1% and a single study on 68 subjects reported a 10.3% long term cure rate. Short- and long-term reoperation rates were not described [667].

Tolerability and safety: Bulking agent associated dysuria and haematuria are frequently reported to be transient and self-resolving [663]. The risk of urinary retention requiring clean intermittent self-catheterisation (CISC), or long-term catheter use is minimal [668]. However, they may provoke allergic reactions [669] and carry a potential risk for migration [670] to proximal and distal lymph nodes [671]. Overall, post procedural urinary retention rates range between 3-17%, with rare need for temporary catheterisation, while post-operatory UTIs ranged from 6-7% [666].

Practical considerations: Bulking agents have shown low cure rates but remain an option for men unfit for more invasive treatment options.

Summary of evidence	LE
There is very limited evidence that bulking agents are effective for the treatment of PPI.	2

Recommendation	Strength rating
Do not offer bulking agents to men with post-prostatectomy incontinence.	Weak

5.6.5.2 Male Slings

Male slings have been introduced to treat mild-to-moderate PPI. However, the definitions of mild and moderate UI are unclear. The majority of studies define cure as 'no pad use' or 'one security pad per 24-hours'. Some authors used more strict criteria such as 'urine loss of less than 2 g per 24-hour pad test' [672].

5.6.5.2.1 Non-adjustable slings

Mechanism of Action: Non-adjustable male slings are positioned under the urethra and fixed by a retropubic or transobturator approach. The tension is adjusted during the surgery, and it cannot be re-adjusted post-operatively. Synthetic slings restore continence in males either by urethral compression and/or by repositioning the bulb of urethra [673, 674].

Efficacy: A SR and meta-analysis involving 33 prospective cohorts and one RCT comparing sling to AUS, reported that both options are effective in improving UI and QoL [675]. Following sling insertion, the overall cure rate was 60% (95% CI: 0.51-0.67) and 56% (95% CI: 0.44-0.68) for sling and AUS respectively. The 24-hour pad use was -3.33 (95% CI: -4.33 to -2.34) and -3.75 (95% CI: -4.56 to -2.93) for slings and AUS, respectively. Similar findings were reported by a network meta-analysis that showed comparable efficacy between slings and AUS [676].

The MASTER Trial, a non-inferiority RCT comparing the outcomes of continence surgery in men with bothersome urodynamic SUI, using a very strict definition of UI after prostate surgery, reported that at twelve-months continence rates were 87% for male sling vs. 84.2% for AUS (95% CI: -11.6-4.6, P_{NI}=0.003]), confirming non-inferiority [677]. The subgroup analysis suggested that male sling is inferior to AUS for men with greater incontinence at baseline (pad weight > 250g); however, the difference did not reach statistical significance.

For the re-positioning sling (AdVance™ and AdVanceXP©), a mean subjective cure rate of 49% (8.6 - 73.7%) after mean follow-up of three years has been reported for 136 patients [678]. A prospective multicentre cohort study, with 60-month follow-up, in men with AdVanceXP demonstrated a constant continence outcome over time with a 57.6% cure rate, 25.4% improvement rate and 16.9% failure rate. These findings were verified in an additional study which reported cure rates of 66.7% and 71.7%, improvement rates of 26.5% and 24.4% and failures rates of 6.9% and 13.3% at 24- and 48-months, respectively [679]. A retrospective comparative study showed that both options are safe and effective in the treatment of male SUI [680].

With the transobturator compressive I-Stop TOMS male sling, 38% of men were dry at twelve months, but this reduced to 23% and 15% after four and five years, respectively [681].

Tolerability and safety: A SR and meta-analysis of 1,170 men with SUI and male sling, reported that the predictors of failure are prior radiation, severity of incontinence and previous surgeries [682]. Pelvic radiotherapy has also been reported in other studies as a negative prognostic factor [683]. A comparison among radiated vs. non-radiated men who had AdVanceXP reported a greater degree of post-operative improvement in the non-radiated group (49.6% vs. 22.2%) as well as greater satisfaction rates (95% vs. 64%) [684]. The most common complication with male slings is pain and local superficial wound infection [685]. Chronic pain has been observed in 1.3% of men who had non-adjustable slings [685]. Post-operative transient voiding dysfunction occurred in 4.3-10.3%, mostly as *de novo* urgency or urinary retention, while erosions and chronic pain were uncommon (0-0.4%), as was explantation [103, 678, 679, 686, 687].

Practical considerations: Fixed male slings are considered safe and improve continence, but their efficacy is limited in men with severe incontinence or previous radiotherapy.

5.6.5.2.2 Adjustable slings in males

Mechanism of Action: Adjustable slings in males are those for which the tension of the sling can be adjusted post-operatively. Three main systems have been used in men: the Remeex® system [688], the Argus® system [689] and the ATOMS® system [690].

Efficacy: There is one small RCT for adjustable slings in males [691]. Most studies consist of prospective or retrospective case series, with variable follow-up and different definitions of success [688, 690-694]. A SR reported objective cure rates varying between 17-92% after adjustable sling implantation [685].

For the Remeex® system, only two studies, with conflicting findings, have been published. One study followed nineteen patients for nearly seven years and reported 70% success, with no explants, infections, or erosions [688]. The second study followed fourteen patients for 25 months. Only 36% of patients were satisfied and multiple re-adjustments were needed. Mechanical failure was reported in 21% [692].

Data on the Argus® system has been reported for 404 men, but only few series have reported on more than 40 patients, with the longest follow-up being 35-months. Success rates varied between 17-93%, with a mean of 73.0% reporting subjective cure [693, 694]. A head-to-head comparison between the two Argus systems reported similar efficacy outcomes at 44 months, but Argus T was associated with a higher inguinal pain and explantation rate [695]. A small study of 22 men with PPI randomised to AdVance or Argus T reported superior 24-hour pad test results and of patient satisfaction levels for Argus T at eighteen-months follow-up [691].

A SR of the ATOMS system reported the pooled evidence from 1,393 patients with a 67% dryness, 90% improvement after adjustment and 16.4% complication rate [690]. The expulsion rate was 5.75%. Another SR and meta-analysis with 3,059 patients reported that ATOMS was superior to ProACT in mean dryness rate (68% vs. 55%), overall improvement (91% vs. 80%), satisfaction rate (87% vs. 56%), mean number of filing adjustments (2.4 vs. 3.5) and post-operative pad use per day (1.1 vs. 2.1) [696].

Tolerability and Safety: The most frequent complications in adjustable male slings are pain, erosions, and infections [685]. Pain at the implant site was usually only temporary, but chronic pain has been reported in 1.5% of men [693, 694]. The number of implants requiring re-adjustment is reported between 8-38.6% [694, 697, 698]. Explantation rates range from 10-15.8% and erosion rate is estimated around 10% [682]. The most common reasons for explantation are device infection (4.1-8%), erosions (4-12%), and urethral perforations (2.7-16%). A SR reported a device explantation rate of 5% vs. 25% and a major complication rate of 4.2% vs. 10.4% for ATOMS and ProACT, respectively [696].

Practical considerations: There is no evidence that adjustability offers additional benefit as RCTs are lacking; therefore, no recommendation can be made at this time. Explantation rate seems superior to fixed male sling based on external comparisons.

5.6.5.2.3 Autologous slings

The strategy of intra-operative placement of an autologous vas deferens sling below the vesico-urethral anastomosis during robotic-assisted radical prostatectomy (RARP) has been explored with the intention to improve early return of continence. Two RCTs [699, 700] showed an advantage of sling vs. no sling at one-month follow-up, and another study [701] showed an advantage of a 6-branch vs. a 2-branch sling at one month follow-up. However, a larger RCT (n=195), showed that continence rate and near-continence rate were similar between groups at six months with 66% vs. 65% and 86% vs. 88%, respectively [702].

Summary of evidence	**LE**
There is limited short-, medium- and long-term evidence that fixed transobturator male slings cure or improve PPI in patients with mild-to-moderate incontinence.	1b
Men with severe incontinence, previous radiotherapy or transurethral surgery may have less benefit from fixed transobturator male slings.	2
There is limited evidence that adjustable male slings can cure or improve SUI in men.	3
There is no evidence that adjustability offers additional benefit over other types of slings.	3
Explantation rate with adjustable male slings seems superior to fixed male sling based on external comparisons.	4
There is no evidence that intra-operative placement of an autologous sling during RARP improves return of continence at six months.	1b

Recommendations	Strength rating
Offer non-adjustable transobturator slings to men with mild-to-moderate* post-prostatectomy incontinence.	Weak
Inform men that severe incontinence, prior pelvic radiotherapy or transurethral surgery may worsen the outcome of non-adjustable male sling surgery.	Weak

** The terms "mild" and "moderate" PPI remain undefined.*

5.6.5.3 Compression devices in males

5.6.5.3.1 Artificial urinary sphincter

Mechanism of action: The AUS is the standard treatment for moderate-to-severe male SUI. The AMS 800 three component system with inflatable cuff, control pump and pressure regulating balloon is the device with the longest follow-up and the greatest level of evidence [703]. The ZSI 375 is a two-component device, inflatable cuff, and control pump, allowing an easier implantation process [704]. Other AUS devices have been launched e.g., the Victo and Br-SL-AS 904 systems but robust evidence regarding their efficacy and safety is pending [705].

Efficacy A meta-analysis of 33 cohort studies and one RCT, reported significant improvement after AUS implantation in overall cure rates (56%) and reductions in pad used per 24-hours (-3.75) [675]. Several observational studies reported on functional outcomes after AMS 800. Social continence rates (0-1 pads used daily) ranged from 55-76.8% [706-708]. A 77.2% continence rate and 89.5% subjective satisfaction rate have been reported after a median follow-up of > fifteen years in 57 men who had undergone AUS placement [709]. A prospective cohort study of 40 patients with a mean follow-up of 53 months, showed that from all urodynamic parameters only low bladder compliance had a negative impact on outcome [710].

However, another retrospective study showed that no urodynamic factors adversely altered the outcome of AUS implantation [711].

Some multicentre studies have confirmed older statements that surgeon's experience and higher surgical volume is associated with better outcomes and a lower revision rate after AUS implantation [712, 713].

The data regarding ZSI 375 is limited. A retrospective, non-randomised trial across several centres in Europe, reported an 84.4% success rate (19.3% dry rate and 65.1% improved 0-1 pads per day) after 43 months [704]. A 72% success rate was reported at seven years follow-up for 45 patients who underwent placement of the ZSI 375 device in France [714].

A retrospective study on 168 patients receiving AUS (AMS 800 AUS system) placements carried out by a single surgeon from 2008 to 2016 at a high-volume academic institution evaluated the causes of AUS failure at a median follow-up from initial placement of 2.7 year. Overall, 63 patients (37.5%) experienced AUS failure requiring device explant/revision. Pressure-regulating balloon malfunction, cuff malfunction, pump malfunction, urethral atrophy, urethral erosion, and infection occurred in 36.5%, 7.9%, 6.3%, 22.2%, 19.0% and 12.7% of all AUS failures, respectively. History of previous pelvic radiotherapy, urethral stricture, urethral sling placement and coronary artery disease were independent predictors of all-cause AUS failure [715].

A retrospective review of all cases of AUS implantation performed between 2005 and 2020 in sixteen different French centres including patients with primary implantation whose indication was moderate to severe SUI after radical prostatectomy (n= 417) or BPO surgery (n=50) found similar social continence rates (zero or one pad per day) at three months between the groups (79% vs. 72%) [716].

Tolerability and safety: Artificial urinary sphincter complications include device infection/erosion (8.5%), mechanical failure (6.2%) and urethral atrophy (7.9%) [717]. In multivariate analysis, radiation therapy was independently associated with risk of urethral atrophy, as were older age and a longer time interval between prostate cancer treatment and AUS surgery [708]. Urethral erosion is associated with previous irradiation and penoscrotal approach [718]. The reported revision rates at three years for any reason were 10-29.1% [706, 718-720]. The risk of urethral erosion after ZSI 375 AUS is 8.2-13.3% and risk of mechanical failure is 2.2-2.5% [704].

A retrospective database comparison found significantly higher complication rates in patients have been reported to be significantly higher in patients undergoing AUS implantation due to UI following BPO surgery compared to patients with post-prostatectomy UI (8% vs. 18%, p=0.044). The same was found for the Clavien-Dindo type 2 complication rate (20.6% vs. 44.4%, p=0.026) [716].

Practical Considerations: Artificial urinary sphincter is efficacious and improves the QoL of men with PPI. To minimise complications, it is advised to refer patients to specialised centres experienced in AUS implementation. Men considering insertion of an AUS should be fully informed that the success of the intervention relies on their ability to operate the pump. Treating physicians should keep in mind that operating the AUS may become difficult in men who develop cognitive impairment or lose manual dexterity. Artificial urinary sphincter has a limited lifespan and 'maintenance' re-operations are common in the long-term. These re-interventions should not be classified as complications [703].

5.6.5.3.2 Non-circumferential compression device (ProACT®)

Mechanism of action: The ProACT® system consists of two devices. Each device includes the balloon, the bi-lumen tubing, and the volume-adjustment port. The devices are introduced by a trocar via two small perineal incisions and are placed under fluoroscopic guidance on each side of the bladder neck, close to the vesico-urethral anastomotic site. The balloons can be filled, and their volume can be adjusted post-operatively using a hypodermic needle injected through the intra-scrotal port.

Efficacy: A SR and meta-analysis of nineteen studies including 1,264 patients reported a 60.2% dry rate, significant reduction in number of pads used per day (-3.1) and greatly improved QoL scores for ProACT® [721]; however, the level of heterogeneity among the included studies was high. A comparison between ATOMS and ProACT®, showed that the former is associated with higher improvement and satisfaction rates and fewer complications [696]. A quasi-randomised trial comparing ProACT® with bone-anchored male slings found that both resulted in similar improvements in SUI (68% vs. 65%, respectively) [722]. A questionnaire study showed that 50% of patients were still significantly bothered by persistent incontinence following ProACT® [723]. A subgroup analysis of radiotherapy patients reported worst outcomes as compared to patients not receiving radiotherapy (46% vs. 68% success rate) as well as a higher percentage of urethral erosion for ProACT® [724].

Tolerability and safety: The most common intra-operative complication during ProACT® implantation is perforation of the bladder and/or urethra. A meta-analysis estimated a perforation rate of 5.3% [721]. The estimated overall revision rate is 22.2%, and the main causes are erosion (3.8%), device leaking (4.1%) and migration (6.5%) [721]. Other prospective series have shown that adverse events were frequent, leading to an explantation rate of 11-58% [722, 723, 725-727].

Practical Considerations: ProACT® has a satisfactory rate of success and seems to be a reasonable alternative for the treatment of male UI; however, it is associated with high complication rates.

Summary of evidence	**LE**
Primary AUS implantation is effective for cure of SUI in men.	1b
Prior pelvic radiotherapy is likely to have a negative impact on the outcomes of AUS implantation.	3
The non-circumferential compression device (ProACT®) is effective for treatment of PPI SUI; however, it is associated with a high failure and complication rate leading to frequent explantation and particularly after pelvic radiation therapy.	2b
The rate of explantation of the AUS due to infection or erosion remains high (up to 24% in some series).	3
Explantation rate with adjustable male slings seems superior to fixed male sling based on external comparisons	4

Recommendations	**Strength rating**
Offer artificial urinary sphincter (AUS) to men with moderate-to-severe stress urinary incontinence.	Strong
Implantation of AUS or ProACT© for men should only be offered in expert centres.	Weak
Warn men receiving AUS or ProACT© that, although cure can be achieved there is a high risk of complications, mechanical failure, and the need for explantation.	Strong
Do not offer non-circumferential compression device (ProACT©) to men who have had pelvic radiotherapy.	Weak

5.6.6 *Surgical treatment for urgency urinary incontinence*

5.6.6.1 *Bladder wall injection of botulinum Toxin-A*

Mechanism of action: The primary mechanism of action of BoNT-A is through the inhibition of neurotransmitter release from cholinergic neurons [556]. OnabotulinumtoxinA (onabotA; BOTOX®) 100 U is licenced in Europe to treat OAB with persistent or refractory non-neurogenic UUI in adults [728, 729].

Efficacy: An RCT of OAB-wet patients whose symptoms were not adequately managed with anticholinergics and who receive either bladder wall injections of onabotA (100 U) or saline reported a 50% reduction in UUI episodes/day whilst the number of micturitions/day reduced by more than two in patients receiving onabotA [730]. A total of 22.9% of the patients in the onabotA arm were fully dry, vs. 6.5% in the saline arm.

A SR and meta-analysis comparing the efficacy of onabotA, mirabegron and anticholinergics in adults with idiopathic OAB reported that patients who received onabotA (100U) achieved greater reduction in UUI episodes, surgery, micturition frequency and the highest odds of achieving dryness as well as >50% reduction from baseline UUI episodes per day [731].

A randomised, placebo-controlled pilot study, assessing the effect of onabotA for the treatment of refractory OAB symptoms after prostatectomy reported significantly improved QoL and ICIQ scores and improvements in daily frequency in patients receiving onabotA compared to placebo [732]. A retrospective trial assessed onabotA efficacy in 65 non-obstructed men with refractory OAB and reported significant improvement in UDI-6 score (-4.2) and IIQ-7 (-6.0) scores, compared to baseline [733].

In a retrospective, single-centre cohort study of onabotA treatment for OAB in 120 patients lead to lower CISC rates in male patients after prior de-obstructive surgery than in surgery-naïve patients (28.6% CISC in the group without prior surgery, 7.5% in the TURP subgroup, and 4.2% in the radical prostatectomy subgroup) [734].

A phase IIIb trial randomised solifenacin-naive patients (10% males) with refractory OAB to onabotA, solifenacin or placebo, and showed that patients receiving onabotA had significantly greater changes in UUI episodes (-3.19) compared to solifenacin (-2.6) and placebo (-1.33) [735].

A network meta-analysis (male population range 9.8-40.2%) which compared onabotA to mirabegron demonstrated that onabotA was associated with improved outcomes in frequency episodes per day (-0.43,[-1.22-0.37]) and in UUI episodes per day (-0.46, [-1.46-0.53]) [736].

Tolerability and safety: Urinary retention and UTIs are the two most common adverse events after onabotA injection. Other reported adverse events include haematuria, dysuria and post-treatment pain [737]. Compared to mirabegron, onabotA is associated with higher risk for UTI and treatment emergent adverse events [736]. A retrospective analysis compared the use of CISC after onabotA injection, among men who had previous prostatectomy vs. those without prior surgery [734]. A 7.5% catheterisation rate after TURP, 4.2% rate after radical prostatectomy and 28.6% rate in men without prior prostate surgery was reported.

Practical Considerations: BoNT-A injections is a recommended treatment option for men with refractory UUI. Despite the lack of a universally accepted injection protocol, gender specific studies and absence of studies in BPO patients, BoNT-A seems superior to medical therapy. It is associated with, higher UTIs and urinary retention risk coupled with the need for repeated injections. A dedicated series in male population, focused on treatment persistence, has shown a high discontinuation rate (68.8%) [738]. Patients treated for OAB with onabotA treatment that have not undergone prior de-obstruction are more likely to develop retention and subsequent CISC.

Summary of evidence	**LE**
A single treatment session of onabotA (100 U) injected in the bladder wall is more effective than placebo at curing and improving UUI/OAB symptoms and QoL.	1b
There is no evidence that repeated injections of onabotA have reduced efficacy, but discontinuation rates are high.	3
There is an increased risk of urinary retention and UTI with onabotA injections.	2

Recommendations	Strength rating
Offer bladder wall injections of onabotulinumtoxinA (100 U) to patients with overactive bladder/urgency urinary incontinence refractory to medical therapy.	Weak
Warn patients of the limited duration of response, risk of urinary tract infection and the possible prolonged need for clean intermittent self-catheterisation (ensure that they are willing and able to do so).	Strong

5.6.6.2 Sacral nerve stimulation (neuromodulation)

Mechanism of action: Sacral neuromodulation (SNM) delivers low amplitude electrical impulses to the sacral nerve roots via an electrode implanted adjacent to the third sacral nerve root and connected to an attached pulse generator implanted in the buttock. It works by modulating neural activity thus stabilising bladder electrical activity through an unknown mechanism. It is a two-stage process: in the first stage, a tined lead electrode is placed percutaneously near the S3 (or if not found, near the S4) root and linked to an external stimulator to assess the response. If symptoms reduced more than 50%, patients are candidates for the second stage which is the full implant.

Efficacy: Several trials assess the clinical effectiveness of SNM. All RCTs suffer from the limitation that patients and assessors cannot be blinded to the treatment allocation since all recruited subjects had to respond to a test phase before randomisation. In addition, the percentage of male population in these trials is around 10%. A meta-analysis compared the effectiveness of SNM to onabotA and reported no significant difference in successfully treated cases at six-month follow-up (RR 0.93; 95% CI: 0.63-1.39) [739].

Tolerability and safety: Main complications after SNM are pain at the implant site (13-42%), lead migration (4.0-21%), leg or back pain (3.0-18%) and wound infection (5.7-6.7%). Surgical revision is required in 29-33% of patients due to device malfunction, battery or device replacement or lead migration [740].

Practical Considerations: SNM represents an alternative to onabotA in patients with refractory OAB, as it has been shown good success rates and an acceptable safety profile.

Summary of evidence	LE
Sacral nerve neuromodulation is effective after failed conservative treatment for OAB/UUI, but no sham controls have been used.	2a

Recommendation	Strength rating
Offer sacral neuromodulation to patients who have urgency urinary incontinence refractory to medical therapy and are willing to undergo surgical treatment.	Weak

5.6.6.3 Cystoplasty/urinary diversion

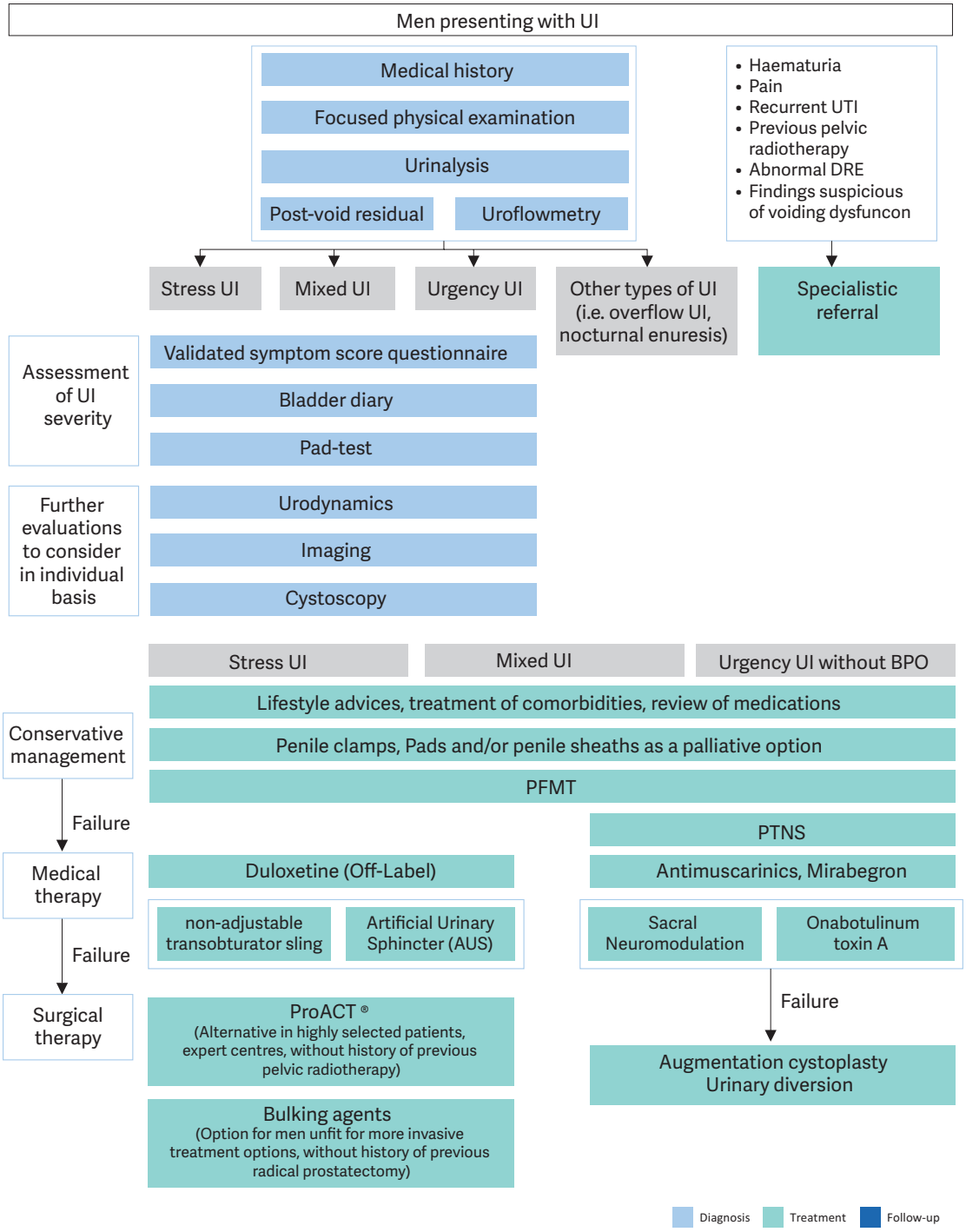
Mechanism of action: Augmentation cystoplasty involves the interposition of a detubularised segment of bowel into the bivalved bladder wall, aiming to increase bladder capacity and reduce OAB related symptoms. Urinary diversion remains a reconstructive option for patients with intractable UUI after multiple pelvic procedures, radiotherapy or pelvic pathology leading to irreversible sphincteric incompetence or fistula formation.

Efficacy: There are no RCTs comparing bladder augmentation to other treatments for patients with refractory OAB/UUI. In a large study with three years follow-up augmentation cystoplasty resulted in a post-operative continence rate of 93% in idiopathic detrusor overactivity patients, 78% in neurogenic overactivity and up to 90% when an AUS was implanted, respectively [741]. The largest case series of bladder augmentation in an idiopathic population included only women [742]. At an average follow up of 75.4 months only 53% were continent and satisfied with the surgery, whereas 25% had occasional leaks and 18% continued to have disabling UUI. A small prospective mixed gender trial reported high patient satisfaction rates with augmentation cystoplasty vs. onabotA therapy [743]. A small study comparing ileal with colonic conduits concluded that there were no differences in the relative risks of UUT infection and uretero-intestinal stenosis [744]. However, there are no studies that have specifically examined these techniques in the treatment of intractable OAB/UUI [744]. Therefore, careful consideration on which operation is undertaken will depend on thorough pre-operative counselling, access to stoma/continence nurses as well as patient factors to allow for fully informed patient choice.

Tolerability and safety: Cystoplasty and urinary diversion are major urological operations. The early post-operative complications include infection, bowel obstruction, bleeding, and cardiorespiratory complications. Long-term complications include metabolic disturbances (hyperchloraemic metabolic acidosis if ileum is used), change in bowel habits, increased mucus production, stone formation, bladder perforation and rarely bladder cancer [745]. Following augmentation cystoplasty or diversion, the majority of patients will depend on self-catheterisation for bladder emptying. Patients with urinary conduit will depend on lifelong urine bags.

Practical Considerations: Augmentation cystoplasty and urinary diversion represent realistic treatment options for men with refractory OAB. However, both options involve a major operation, with a non-negligible long-term complication rate and a lifelong reliance on catheterisation or urine bags.

Figure 6. Evaluation and Management of Urinary Incontinence in non-neurogenic Male LUTS



DRE = digital-rectal examination; UI = urinary incontinence; UTI = urinary tract infection; PFMT = pelvic floor muscle training; PTNS = posterior tibial nerve stimulation; BPO = benign prostatic obstruction.

Summary of evidence	LE
There is limited evidence of the effectiveness of augmentation cystoplasty and urinary diversion in treatment of idiopathic OAB.	3
The need to perform CISC following augmentation cystoplasty is high.	3
Augmentation cystoplasty and urinary diversion are associated with high risks of short- and long-term complications.	3
There is no evidence comparing the efficacy or adverse effects of augmentation cystoplasty to urinary diversion.	3

Recommendations	Strength rating
Offer augmentation cystoplasty to patients with overactive bladder (OAB)/urgency urinary incontinence (UUI) who have failed all other treatment options and are able and willing to perform self-catheterisation.	Weak
Inform patients undergoing augmentation cystoplasty of the high risk of complications; the risk of having to perform clean intermittent self-catheterisation and the need for life-long surveillance.	Strong
Only offer urinary diversion to patients who have failed less invasive therapies for the treatment of OAB/UUI, who will accept a stoma.	Weak

5.7 Management of underactive bladder

5.7.1 *Epidemiology and Pathophysiology*

Various definitions of underactive bladder (UAB) and detrusor underactivity (DU) can be identified in the current literature. DU appears as the most consistent concept, is based on urodynamics, and is defined by the International Continence Society as *"a contraction of reduced strength and/or duration, resulting in prolonged bladder emptying and/or failure to achieve complete bladder emptying within a normal time span"* [17]. Underactive bladder is a terminology that should be reserved for describing symptoms and clinical features related to DU. A tentative definition has been proposed as *"a symptom complex suggestive of detrusor underactivity and usually characterized by prolonged urination time with or without a sensation of incomplete bladder emptying, usually with hesitancy, reduced sensation on filling, and a slow stream"* [746].

The prevalence of DU in the general population is unknown, as men with DU are either asymptomatic or have non-specific LUTS. In clinical studies of men with non-neurogenic LUTS referred for video-urodynamic studies, the prevalence of DU has been reported to be 10% [747, 748] ranging up to 48% in the elderly (≥ 70 years) [749]. Detrusor underactivity is a chronic condition, but its natural history in untreated men has shown a plateau-like course with few symptomatic and urodynamic changes over time [750].

Healthy voluntary bladder muscle contraction requires a functional detrusor muscle, intact efferent and afferent innervation, and integrated central neural control mechanisms. Dysfunction of any of these essential components can lead to DU, which may be the consequence of various pathological processes, suggesting a multifactorial pathophysiology.

Neurogenic. Neurogenic DU may be the consequence of peripheral or central nervous system disease. This aetiology is covered in the EAU Guidelines on Neuro-Urology [751].

Myogenic. Several conditions can affect the myocytes or their extracellular matrix, resulting in attenuated detrusor contraction. Bladder outflow obstruction and diabetic cystopathy are common causes of myogenic DU. However, many aspects of the pathophysiology of myogenic DU that relate to BOO and diabetic cystopathy are mainly based on animal studies and the clinical picture in any individual patient is probably multifactorial in nature [752, 753]. Some SRs have addressed the role of chronic BOO on bladder dysfunction in humans. Aside from the impact on smooth muscle cells, multiple other consequences were identified including modifications on the extracellular matrix, and damage to the urothelium, suburothelium and bladder innervation. To date, BOO-related DU pathophysiology remains poorly understood [754].

Iatrogenic. Patients may experience DU following pelvic surgery (e.g., radical prostatectomy or extended rectal surgery) and/or radiation therapy [752]. Pharmacological treatments (e.g., drugs with anticholinergic effects or opioids) may also be involved in the impairment of detrusor contractility [752].

Idiopathic. Given the higher prevalence of DU in the elderly, it has been hypothesised that ageing would be a major contributor. However, available data do not provide strong evidence to support the assertion that detrusor contractile function declines with common ageing [752].

5.7.2 ***Diagnostic Evaluation***

5.7.2.1 Medical history and physical examination

A review of medical history, including co-morbidities and current medications, can identify potential causes of UAB. The history should also include a thorough evaluation of LUTS, which should be classified into storage, voiding and post-micturition symptoms. There is no pivotal symptom to identify patients with UAB. The clinical presentation ranges from asymptomatic cases to symptomatic chronic urinary retention. Since UAB is a disorder of the voiding phase, voiding symptoms are to be the predominant ones, but they may be associated with storage symptoms, particularly in case of incomplete bladder emptying or other concomitant bladder dysfunctions [755].

Clinical diagnosis is even more difficult when patients have other conditions that may affect the presentation of LUTS, such as known or suspected BOO/BPO. In this setting, there is no validated tool to ascertain the respective roles of DU and BOO on voiding symptoms.

The Bristol group was the first to attempt to identify systematically which of the LUTS are most closely related to UAB [756]. Men with UAB reported a statistically significantly higher occurrence of decreased and/or interrupted urinary stream, hesitancy, feeling of incomplete bladder emptying, palpable bladder, feeling of incomplete bowel emptying, absent and/or decreased sensation, and always straining to void compared with men with normal pressure-flow studies. Several authors have proposed predictive models based on the patient's LUTS to distinguish individuals with an UAB from patients with normal pressure-flow studies or BOO [757, 758]. However, there is no conclusive evidence that one prognostic model is more accurate than another, and there is no published external validation of these models.

5.7.2.2 Questionnaires

There is no specific validated questionnaire for the diagnosis of UAB. Physicians can refer to validated questionnaires for male LUTS, but their clinical benefit to monitor symptom changes and treatment in patients with UAB is uncertain [759].

5.7.2.3 Uroflowmetry

Some authors have proposed to distinguish UAB from BOO based on uroflowmetry parameters, not only on Q_{max}, but on flow patterns and combinations of scores [760, 761]. The diagnostic accuracy of the developed models remains to be established and external validation is lacking.

5.7.2.4 Ultrasound scan and post-void residual measurement

Ultrasound findings have been evaluated as non-invasive predictors of DU. In a single-centre prospective study including 143 adult males with LUTS, detrusor wall thickness ≤ 1.23 mm and bladder capacity > 445 mL was associated with urodynamically proven DU, with sensitivity and specificity of 42% and 100%, respectively [762].

Detrusor underactivity is often associated with prolonged bladder emptying time and/or post-void residual urine. However, while high PVR value have been associated with presence of DU, no consensus cut-off has been identified to diagnose DU and it is unlikely that one will ever exist [763].

5.7.2.5 Urodynamics

Underactive bladder is a clinical diagnosis based on sign and symptoms and DU is a term that should be reserved for a urodynamic diagnosis [764]. Invasive urodynamics is the only widely accepted method for diagnosing DU [755]. However, current data do not allow for a consensus definition of the urodynamic criteria to be used for the diagnosis of DU. Three algorithms, which are all based on computer-urodynamic investigation and quantification of detrusor pressure during voiding, have been suggested to quantify detrusor power [763]:

- Griffiths' Watt factor: quantification of detrusor power with a formula consisting of detrusor pressure during voiding, contraction speed, and bladder volume at each point of micturition, expressed as W/m2. Detrusor power varies during voiding, single calculations are usually offered on urodynamic evaluation sheets, for example, maximum detrusor power (W_{max}) or detrusor power at maximum flow (WQ_{max}). However, it remains controversial which of the calculations and what threshold value should be used. Expert opinion suggested using a W_{max} threshold value of 7.0 W/m2 [763].
- Schafer's detrusor-adjusted mean PURR factor (DAMPF): detrusor power can grossly be quantified as very weak, weak, normal, or strong if linearised passive urethral resistance (linPURR) is drawn into the Schafer

nomogram. The length of linPURR determines detrusor strength.

- Bladder contractility index (BCI): quantification of detrusor power/contractility can be derived from Schafer's linPURR lines and calculated by the formula: BCI=pdetQ_{max} + 5Q_{max}. BCI>150 describes strong contractility, 100-150 normal contractility, and <100 weak contractility. Currently the BCI is the most widely used in the literature and clinical trials.

None of these models are validated and their concordance for the diagnosis of DU is uncertain [765, 766], preventing a consensus to be reached on the optimal method for diagnosing DU. Furthermore, detrusor contraction strength is only one aspect of voiding efficiency, and future models will need to encompass several aspects of assessing detrusor contraction (e.g., strength, durability) as well as how the bladder empties.

*5.7.3 **Conservative management***

In general, the treatment of UAB should focus on symptom relief, avoiding complications (such as infections) and improving or at least maintaining QoL. It involves a pragmatic approach ensuring timely bladder drainage by trying to improve bladder contraction and/or decrease urethral resistance [763].

5.7.3.1 Behavioural interventions

There are no randomised studies or large high-quality studies available investigating the effect of behavioural interventions in male patients with UAB. The main goal is to reduce bothersome symptoms and prevent complications of incomplete bladder emptying (such as recurrent UTI) while avoiding invasive treatments. Asymptomatic patients at risk of UAB should be informed of this, (like diabetes mellitus or after pelvic surgery/ radiotherapy) as diagnosis is delayed due to loss in bladder sensation and enlarged bladder capacity. In patients with sensory impairment, timed or scheduled voiding schemes can be recommended. In patients with bothersome frequency, double or triple voiding as well as Valsalva or the Credé maneuver can reduce PVR and may improve their symptoms however no clinical trial has proven efficacy or harm of these measures in the non-neurogenic male population.

A descriptive cohort investigated male patients with DU started on conservative treatment (not further defined) and the need for clean intermittent catheterisation (CIC) after five years. They concluded that male patients with non-neurological DU can remain stable without the need to initiate CIC. No urodynamic risk factors for CIC were detected [767].

5.7.3.2 Pelvic floor muscle relaxation training with biofeedback

Successful voiding is initiated by relaxation of the pelvic floor and urinary sphincter. A failure of at least one of these mechanisms can result in voiding dysfunction as well as inhibition of detrusor contraction, which is called the guarding reflex [768]. Therefore, physiotherapy with pelvic floor muscle relaxation is usually a first line therapy for voiding dysfunction but no RCT in male adults investigates its effect on UAB. Evidence is derived mostly from paediatric studies. One RCT in children compared the effect of standard urotherapy (diet, adapted fluid intake and timed voiding + toilet training) with animated biofeedback therapy versus urotherapy alone in children with proven DU. Improvement was seen in PVR, recurrent UTI and urodynamic parameters, like flow curve and maximum flow rate, in both treatment groups, but improvement was significantly better at all stages in children receiving biofeedback [769].

5.7.3.3 Clean intermittent self-catheterisation (see section 5.6.3.1.4)

In patients with persistently elevated PVR, clean intermittent catheterisation (CIC) is the preferred method for complete and timely bladder drainage. No data exist on the maximum accepted PVR but after 300 mls the risk of UTIs increases [770]. Clean intermittent self-catheterisation is preferred over indwelling catheters, as it might reduce the risk of complications like UTI, bacterial colonisation, bladder stones and overflow incontinence. However, this technique demands a certain level of manual dexterity and cognition if performed by individuals themselves or it can be performed by a caregiver or second person, for example a partner. More details can be found in section 5.6.3.1.4.

5.7.3.4 Indwelling catheters

Indwelling catheters should be avoided in the long-term unless other treatment options are not indicated, and the patient is unwilling or unable to perform CIC and there is no one else that can perform it for them. In this case, suprapubic catheters are preferred over urethral catheters due to the risk of traumatic hypospadias [620]. For further details see section 5.6.3.1.4.

5.7.3.5 Intravesical electrical stimulation

Intravesical electrotherapy (IVES) is an electrical stimulation technique that stimulates the A-delta mechanoreceptor afferents thereby reinforcing bladder contractions. Therapy consists of daily sessions of

stimulation with ten to fifteen sessions considered as a trial period. Afferent circuits should be intact together with a healthy detrusor muscle. A recently published RCT in a mixed-gender population with neurogenic predominant UAB, reported improvement at four weeks after IVES compared to sham in PVR (-97ml vs. -10.5ml, $p < 0.01$), in bladder voiding efficiency (+13.3 vs. 0.0, $p<0.01$) and in Q_{max} (+1.3 vs. +0.2, $p < 0.04$) [771]. One small retrospective study with a mixed population (eleven women - five men) showed some improvement in voiding after IVES in two-third of the study population [772]. Other evidence is mainly derived from small studies in children [755]

5.7.3.6 Extracorporeal Shock Wave Therapy

Extracorporeal Shock Wave therapy (ESWT) improves neovascularisation and tissue regeneration and theoretically could improve detrusor contractility. A small placebo controlled-RCT reported significant improvements in PVR and UAB-Q scores at 4th week but not at 12th week of follow up [773, 774].

Summary of evidence	**LE**
Behavioural interventions can be attempted in men with UAB and high PVR. Avoid increasing intrabdominal pressure, with Valsalva or Credé, in those with poorly compliant bladders.	3
Pelvic floor muscle relaxation techniques can help with voiding dysfunction.	4
Clean intermittent catheterisation is first line therapy in men with UAB and high PVR over 300ml.	3
Indwelling catheters (urethral or suprapubic) are associated with a range of complications as well as an enhanced risk of UTI.	3
If indwelling catheters are the treatment choice, then the suprapubic route is favoured over urethral due to risk of traumatic hypospadias.	3

Recommendations	**Strength rating**
Initiate clean intermittent self-catheterisation if there is risk of upper tract damage or PVR is > 300ml.	Weak
Offer indwelling transurethral catheterisation or suprapubic cystostomy only when other modalities for urinary drainage have failed or are unsuitable.	Weak

5.7.4 ***Pharmacological management***

5.7.4.1 Parasympathomimetics

For the mechanism of action of parasympathomimetics, see section 5.2.3.

A SR and meta-analysis were performed in both male and female patients with UAB evaluating twelve RCTs on the use of both subgroups (muscarinic agonists and acetylcholinesterase inhibitors) of parasympathomimetics [775, 776]. The meta-analysis showed a small benefit in some patients with (post-procedure) urinary retention with no increase in adverse events, but without improvement of PVR. However, the results of this SR are confounded by the low number of small studies, weak data, high heterogeneity and a very short-term follow up. Therefore, based upon the available literature, no strong evidence-based conclusions can be drawn on the role of parasympathomimetics as an effective pharmaceutical treatment for UAB.

5.7.4.2 Alpha-adrenergic blockers

One alternative to improve bladder emptying and micturition is by reducing outflow resistance in patients with UAB. Although there is a lack of high quality RCTs, some evidence exists that lowering outflow resistance improves voiding functions and bothersome symptoms in men with UAB. A single-blind prospective RCT investigated 119 patients with UAB treating them with a cholinergic drug, an alpha-adrenergic blocker or both. They showed both a significant improvement in symptoms as well as PVR and flow rate in patients treated with combination therapy compared to monotherapy [777]. A study evaluated the effects of tadalafil (a PDE5 inhibitor) and silodosin on voiding function in male patients with non-neurogenic DU. After propensity score matching, they showed improvement of both QoL and UDS parameters and voiding parameters in both subgroups [757]. Overall, the clinical rigor required to provide evidence-based support for the use of this class of medications in treating UAB is still lacking.

5.7.4.3 Prostaglandins

Prostaglandins are involved in the modulation of bladder function. There are five subtypes, of which prostaglandins E2 and F2a appear to be predominant in stimulating detrusor contractions. A Cochrane review analysing three RCTs using intravesical instillation of PGE2 and PGF2a, suggests a reduction of postoperative

retention after catheter removal [778]. However due to methodological limitations of the included trials, the use in clinical practice remains uncertain. One placebo-controlled trial investigated the combination of intravesical PGE2 with bethanechol chloride in nineteen patients with UAB [779]. Although they showed a reduction in PVR compared to placebo, clinical relevance is questioned. Overall, the efficacy of the prostaglandin agents in treating UAB is not established.

5.7.4.4 Other drugs

As previously stated, treatment with PDE5 inhibitors (such as tadalafil) showed improvement of both QoL and UDS parameters and voiding parameters in male patients with UAB [757]. For more information on PDE5s, please see section 5.2.5.

Summary of evidence	LE
Evidence on the effect of parasympathomimetics on clinical or urodynamic parameters of UAB is lacking. Possible serious adverse effects should be considered before administration.	4
There is limited evidence about effectiveness of alpha-adrenergic blockers in men with UAB.	4
The efficacy of the prostaglandin agents in treating UAB is not established.	4

Recommendations	Strength rating
Do not routinely recommend parasympathomimetics for treatment of men with underactive bladder.	Strong
Offer alpha-adrenergic blockers before more-invasive techniques.	Weak

5.7.5 ***Surgical treatment for underactive bladder***

Surgical options for male patients with non-neurogenic UAB/DU include benign prostatic surgery and sacral neuromodulation [165, 780-786].

5.7.5.1 Surgery for benign prostatic obstruction

A SR evaluated the outcomes of surgery for benign prostatic obstruction in men with pre-operative DU or acontractile detrusor [165]. Mean total IPSS variation following surgery was reported to range from -3 to -19.5 points. A >3 points improvement in terms of total IPSS score was evident in fourteen studies included into the SR [165]. Mean IPSS QoL score variation ranged from -0.9 to -3 points [165]. Mean maximum urinary flow (Q_{max}) improvement ranged from +1.4 to +11.7 mL/s. Mean PVR improvement ranged from -16.5 to -736 mL [165].

Direct comparisons between patients with DU versus without DU provided conflicting results [165]. A study found that post-operative outcomes one month after photoselective laser vaporisation prostatectomy (PVP) were worse in patients with DU compared to patients without DU [40]. In men with pre-operative DU, mean total IPSS score improved from 12.0 to 15.2, mean Q_{max} improved from 4.8 ml/sec to 8.2 ml/sec, and mean PVR improved from 918.3 mL to 325.9 mL. In patients without pre-operative DU mean total IPSS improved from 17.5 to 9.7, mean Q_{max} improved from 6.9 ml/sec to 17.6 ml/sec, and mean PVR improved from 225.0 mL to 99.2 mL [783]. A statistically significant difference ($p \leq 0.05$) was observed in terms of mean IPSS, mean Q_{max}, and mean PVR when comparing patients with and without pre-operative DU at one month follow-up [783].

Similarly, another study found that patients with DU had smaller decrease in terms of median total IPSS (-6.5 vs. -11) and a smaller increase in the Q_{max} (+3.5 mL/s vs. +8.2 mL/s) after PVP than did those without DU [782]. In details, in men with DU median total IPSS score improved from 17.5 to 9.5, median Q_{max} improved from 9.7 ml/sec to 13.8 ml/sec and median PVR improved from 28 mL to 11.5 mL. In patients without pre-operative DU median IPSS improved from 20.5 to 8, median Q_{max} improved from 10 ml/sec to 17.9 ml/sec, and median PVR improved from 27.5 mL to 9 mL [782]. Statistical analysis found a significant differences between the two groups at follow-up evaluations only in terms of Q_{max} (p: 0.023).

Other authors failed to find differences in terms of symptom improvement and success rates between patients with and without pre-operative DU [165]. Mean Bladder Contractility Index (BCI) improvement was reported to range from 4 to 44.6 [165].

A retrospective study found that 81.7% of patients with DU or acontractile detrusor undergoing TURP or TUIP achieved a satisfactory treatment outcome defined as improved QoL and voiding efficiency of >50% [784]. Among these patients, mean BCI significantly increased from 16.4 to 61.0 and 69.4% of them had recovery of detrusor function within 3 months [784].

A prospective case series found that 78% of patients with DU or acontractile detrusor and concurrent BPO undergoing holmium laser enucleation of the prostate exhibited significant return of bladder contractility, determined by the presence of a sustained, volitional detrusor contraction at six months follow-up [785]. Of note, 94.7% of patients were voiding spontaneously with acceptable PVR volume, whereas 5.3% required CIC post-operatively [785].

Factors influencing the surgical outcomes have been investigated: older age, lack of obstruction, concomitant detrusor overactivity, lower detrusor contractility and use of transurethral resection of the prostate or photovaporisation instead of holmium laser enucleation of the prostate (HoLEP) were associated with worse outcomes [165].

A retrospectively investigated the effect of DU on the efficacy of TURP by comparing the subjective and objective parameters preoperatively and three months post-operatively between severe (BCI < 82), mild (82 ≤ BCI < 100), and absent DU (BCI ≥ 100) in two obstruction groups (20 ≤ Bladder Outlet Obstruction Index (BOOI) < 40 and BOOI ≥ 40) [786]. Successful improvement after the operation were defined according to the criteria developed by Homma *et al.* [786]. In patients with pre-operative BOOI ≥ 40 the successful improvement rates for the IPSS, IPSS-Storage, IPSS-Voiding, QoL and free Q_{max} were 60.6%, 54.5%, 54.5%, 63.6% and 66.6% in patients with severe DU. The same figures in patients with BOOI ≥ 40 and mild DU were: 87.7%, 63.2%, 94.7%, 75.4%, and 75.4%, respectively. Finally, in patients with BOOI ≥ 40 and absent DU the successful improvement rates were 94.1%, 82.8%, 95.6%, 90.6%, and 71.4%, respectively.

In the 20 ≤ BOOI < 40 group, the successful improvement rates for the IPSS, IPSS-Storage, IPSS-Voiding, QoL and free Q_{max} in the severe DU patients were only 38.2%, 38.2%, 44.1%, 41.2% and 38.2%, respectively. The same figures in patients with mild DU were: 83.3%, 66.7%, 83.3%, 75.0%, and 41.7%, respectively. Finally, in patients with absent DU the successful improvement rates were 90.9%, 90.9%, 90.9%, 90.9%, and 81.8%, respectively.

Therefore, patients with varying degrees of benign prostate obstruction can benefit from TURP, but for patients with severe DU in the 20 ≤ BOOI < 40 group, TURP should be carefully considered only after adequate counselling [786].

Unfortunately, the few long-term data available seem to reveal poor durability of benefits [165].

5.7.5.2 Sacral neuromodulation

Sacral neuromodulation (SNM) has been reported to improve idiopathic urinary retention in women in long-term studies [787]. However, only scarce evidence exists in men with DU or acontractile detrusor. A multicentric, retrospective case series reported the outcomes of SNS in adults with a urodynamic-based diagnosis of DU and symptom duration of more than six months who failed to respond to first and second-line treatment options [781]. Patients with cognitive disabilities, BOO and those who had any contraindication for SNS were excluded. Overall, 35 males were included. Of these, 51.4% responded to the first stage and were candidates for the full implant. Overall, 72% of male patients had favourable responses after the full implantation. Voided volume, PVR, and the median Q_{max} improved in both sexes [781]. In men who underwent full implantation voided volume improved from 75.0 mL to 300.0 mL, PVR improved from 350.0 mL to 90.0 mL, and mean Q_{max} improved from 7.0 to mL/sec to 16.0 mL/sec. Evidence from another retrospective study suggests that residual detrusor contractility is more likely to respond to a trial of SNM compared to detrusor acontractility [788].

Summary of evidence	**LE**
In patients with DU or acontractile detrusor and concomitant benign prostatic obstruction, de-obstruction procedures are associated with improvements in bladder contractility index, mean total International Prostate Symptom Score, mean maximum urinary flow, and mean postvoid residual volume.	3
Older age, lack of bladder outflow obstruction, concomitant detrusor overactivity, lower bladder contractility and use of transurethral resection of the prostate or photo vaporisation instead of laser enucleation of the prostate are associated with worse post-operative outcomes after de-obstruction procedures.	3
Sacral neuromodulation provides statistically significant improvement in terms of voided volume, post-void residual, and median maximum flow rate in men with refractory DU and no BPO.	3

Recommendations	Strength rating
Counsel patients with evidence of detrusor underactivity (DU) or acontractile detrusor and concomitant benign prostatic enlargement about the potential subjective and objective benefits of benign prostatic surgery.	Weak
Offer men with DU and no benign prostatic obstruction, test phase sacral neuromodulation.	Weak

*5.7.6 **Follow-up***

The natural history and clinical evolution at long-term follow-up of men with UAB is not well documented. A small retrospective cohort evaluated recovery of detrusor contraction one year after (medical or surgical) treatment through video-urodynamic studies [789]. In this small cohort, bladder contractility recovery was seen in 43.9% of patients and an optimal bladder compliance cut-off value of < 80ml/cmH2O was predictive of better recovery. The interval between follow-up visits depends on patient characteristics, treatments given and the frequency of urinary complications. Two studies looked at the natural evolution of detrusor contractility with or without TURP for BOO [108, 750]. Although retrospective, they showed that detrusor contractility does not get worse with persisting BOO nor that it improves after performing a TURP. The underactive detrusor seems to remain under-active but does not deteriorate with time.

6. FOLLOW-UP

6.1 Watchful waiting (behavioural)

Patients who elect to pursue a WW policy should be reviewed at six months and then annually, provided there is no deterioration of symptoms or development of absolute indications for surgical treatment. The following are recommended at follow-up visits: history, bladder diary, IPSS/ICIQ-MLUTS, uroflowmetry, and PVR volume.

6.2 Medical treatment

Patients receiving α1-blockers, muscarinic receptor antagonists, beta-3 agonists, PDE5Is or the combination of α1-blockers and 5-ARIs or muscarinic receptor antagonists should be reviewed four to six weeks after drug initiation to determine the treatment response. If patients gain symptomatic relief in the absence of troublesome adverse events, drug therapy may be continued. Patients should be reviewed at six months and then annually, provided there is no deterioration of symptoms or development of absolute indications for surgical treatment. The following are recommended at follow-up visits: history, IPSS/ICIQ-MLUTS, uroflowmetry, and PVR volume. Frequency volume charts or bladder diaries should be used to assess response to treatment for predominant storage symptoms or nocturnal polyuria.

Patients receiving 5-ARIs should be reviewed after twelve weeks and six months to determine their response and adverse events. The following are recommended at follow-up visits: history, IPSS/ICIQ-MLUTS, uroflowmetry and PVR volume. Men taking 5-ARIs should be followed up regularly using serial PSA testing if life expectancy is greater than ten years and if a diagnosis of PCa could alter management. A new baseline PSA should be determined at six months, and any confirmed increase in PSA while on 5-ARIs should be evaluated.

In patients receiving desmopressin, serum sodium concentration should be measured at day three and seven, one month after initiating therapy and periodically during treatment. If serum sodium concentration has remained normal during periodic screening follow-up screening can be carried out every three months subsequently. However, serum sodium concentration should be monitored more frequently in patients ≥ 65 years of age and in patients at increased risk of hyponatremia. The following tests are recommended at follow-up visits: serum-sodium concentration and FVC. The follow-up sequence should be restarted after dose escalation.

6.3 Surgical treatment

After prostate surgery, patients should be reviewed four to six weeks after catheter removal to evaluate treatment response and adverse events. If patients have symptomatic relief and are without adverse events, no further re-assessment is necessary. The following tests are recommended at follow-up visit after four to six weeks: IPSS/ICIQ-MLUTS, uroflowmetry, erectile and ejaculatory function and PVR volume.

Summary of evidence	LE
Follow-up for all conservative, medical, or operative treatment modalities is based on empirical data or theoretical considerations, but not on evidence-based studies.	4

Recommendations	Strength rating
Follow-up all patients who receive conservative, medical, or surgical management.	Weak
Define follow-up intervals and examinations according to the specific treatment.	Weak

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8. CONFLICT OF INTEREST

All members of the EAU Non-neurogenic Male LUTS Guidelines Panel have provided disclosure statements of all relationships that they have that might be perceived as a potential source of a conflict of interest. This information is publicly accessible through the European Association of Urology website: http://uroweb.org/guideline. This guidelines document was developed with the financial support of the European Association of Urology. No external sources of funding and support have been involved. The EAU is a non-profit organisation and funding is limited to administrative and travel and meeting expenses. No honoraria or other reimbursements have been provided.

9. CITATION INFORMATION

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The compilation of the complete Guidelines should be referenced as:
EAU Guidelines. Edn. presented at the EAU Annual Congress Paris April 2024. ISBN 978-94-92671-23-3.

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Management of Non-Neurogenic Female Lower Urinary Tract Symptoms

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1. INTRODUCTION

Lower urinary tract symptoms (LUTS) encompass storage, voiding and post-micturition symptoms [1]. Storage symptoms include frequency, urgency, nocturia and urinary incontinence (UI) (stress UI [SUI], urgency UI [UUI], and mixed UI [MUI]). Voiding symptoms include hesitancy, intermittency, slow stream, straining, splitting or spraying of the urinary stream and terminal dribble. Post-micturition symptoms include post-void dribbling and feeling of incomplete bladder emptying. Lower urinary tract symptoms are often broadly classified into clinical syndromes/entities such as overactive bladder (OAB), underactive bladder (UAB), UI, nocturia, dysfunctional voiding, or genitourinary fistulae.

Lower urinary tract symptoms are common in women [2-5] and cause a great deal of distress and embarrassment [6], as well as significant costs to both individuals and society [7]. Estimates of prevalence vary according to the definition and population studied. However, there is universal agreement about the importance of the problem in terms of human suffering and economic cost [7].

1.1 Aim and objectives

These Guidelines from the European Association of Urology (EAU) Working Panel on Non-neurogenic Female LUTS are written by a multidisciplinary group, primarily for urologists, but are likely to be referred to by other professional groups. The guidelines aim to provide sensible and practical evidence-based guidance on the clinical problems associated with female LUTS rather than an exhaustive narrative review. Such reviews for UI and other LUT syndromes are already available from the International Consultation on Incontinence (ICI) [8] and other sources. Therefore, these EAU Guidelines do not describe the causation, basic science, epidemiology and psychology of LUTS/UI in detail. The focus of these guidelines is on assessment and treatment, reflecting clinical practice, and they do not consider women with LUTS caused by neurological disease, or LUTS occurring in children, as these are covered by complementary EAU Guidelines [9, 10].

The current guidelines provide:

- A clear description of the assessment and treatment of common clinical problems. This can provide the basis for both individual patient management and 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 in those areas of practice for which there is little or no high-quality evidence.

The guideline has seen a significant expansion of scope from UI to non-neurogenic female LUTS in recent years. The primary consideration here is to include the significant population of women with functional urological conditions not necessarily associated with UI that were hitherto not accounted for in previous guidelines. Secondary considerations are to align more cohesively with the existing Non-neurogenic Male LUTS Guidelines. As a consequence of the anatomical and physiological differences between the male and female LUT, the prevalence, pathophysiology, diagnostic approach and management of male and female LUTS differ widely. For that reason, the EAU Guidelines Office decided to provide gender-specific guidelines on LUTS and UI.

1.2 Panel composition

The EAU Non-neurogenic Female LUTS Panel consists of a multidisciplinary group of experts, including urologists, a uro-gynaecologist, a urodynamic scientist, a physiotherapist, a nurse practitioner in Continence Care, and patient advocates. All experts involved in the production of this document have submitted potential conflict of interest statements that can be viewed on the EAU website: https://uroweb.org/guidelines/non-neurogenic-female-luts/panel.

1.3 Available publications

A quick reference document (Pocket Guidelines) is available in print. This is an abridged version that require consideration together with the full-text versions. All documents are accessible through the EAU website: https://uroweb.org/guideline/non-neurogenic-female-luts/.

1.4 Publication history

The first EAU Urinary Incontinence Guidelines were published in 2001. The guidelines have been modified since to broaden its scope specifically to include other female LUTS as of 2021. All sections of the 2023 Female LUTS Guidelines have been fully updated. The next update of the Female LUTS Guidelines will be published in 2025.

2. METHODS

2.1 Introduction

For the 2023 Non-neurogenic Female Lower Urinary Tract Symptoms guidelines, databases searched included Medline, Embase, and the Cochrane Libraries, covering a time frame between 01 September 2021 and 20 February 2022, with a focus on high-level evidence only (systematic reviews (SR) and meta-analyses). A total of 345 unique records were identified, retrieved, and screened for relevance. Detailed search strategies are available: https://uroweb.org/guideline/non-neurogenic-female-luts/?type=appendices-publications.

For the 2023 edition of the guidelines a de novo systematic review was undertaken by the Panel on the subject of OAB syndrome [11]. The results from this publication have informed the corresponding sections of this guidelines update.

Recommendation within the Guidelines are developed by the panels to prioritise clinically important care decisions. The strength of each recommendation is determined by the balance between desirable and undesirable consequences of alternative management strategies, the quality of the evidence (including certainty of estimates), and the nature and variability of patient values and preferences [12, 13]. This decision process, which can be reviewed in the strength rating forms which accompany each guideline statement, addresses a number of key elements:

1. the overall quality of the evidence which exists for the recommendation [14];
2. the magnitude of the effect (individual or combined effects);
3. the certainty of the results (precision, consistency, heterogeneity and other statistical or study related factors);
4. the balance between desirable and undesirable outcomes;
5. the impact of patient values and preferences on the intervention.

Strong recommendations typically indicate a high degree of evidence quality and/or a favourable balance of benefit to harm and patient preference. Weak recommendations typically indicate availability of lower quality evidence, and/or equivocal balance between benefit and harm, and uncertainty or variability of patient preference [15].

Additional information can be found in the general Methodology section of this print, and online at the EAU website: https://uroweb.org/guidelines/policies-and-methodological-documents/.

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

2.2 Review

The guidelines were extensively peer reviewed prior to publication in 2021.

2.3 Future goals

- Systematic review of underactive bladder (UAB) in women.

3. DIAGNOSIS

3.1 History and physical examination

Taking a thorough clinical history is fundamental to the process of clinical evaluation. Despite the lack of high-level evidence to support it, there is universal agreement that taking a history should be the first step in the assessment of anyone with LUTS. The history should include a full evaluation of LUTS, as well as sexual, gastrointestinal, and neurological symptoms. The history should help to categorise LUTS as storage, voiding and post-micturition symptoms, and classify UI as SUI, UUI, MUI or overflow incontinence; the latter being defined as “the complaint of UI in the symptomatic presence of an excessively (over-) full bladder (no cause identified)” [16].

The history should also identify patients who need referral to an appropriate clinic/specialist. These may include patients with associated pain, haematuria, history of recurrent urinary tract infection (UTI), pelvic surgery or radiotherapy, constant leakage suggesting a fistula (see Section 4.8), new-onset enuresis or suspected neurological disease. A neurological, obstetric, and gynaecological history may help to understand

the underlying cause and identify factors that may affect treatment decisions. Guidance on history-taking and diagnosis in relation to UTIs, neuro-urological conditions and chronic pelvic pain (CPP) can be found in the relevant EAU Guidelines [9, 17, 18]. Patients should also be asked about other co-morbidity as well as smoking status, previous surgical procedures, and current medications, as these may affect LUTS.

There is also little evidence from clinical trials that carrying out a clinical examination improves outcomes, but widespread consensus suggests that clinical examination remains an essential part of assessment of patients with LUTS. Examination should include abdominal examination, to detect an enlarged urinary bladder or other abdominal mass, and digital examination of the vagina and/or rectum. Pelvic examination in women includes assessment of oestrogen status, pelvic floor muscle (PFM) function and careful assessment of any associated pelvic organ prolapse (POP). A cough stress test is necessary to look for SUI. Among women with genital prolapse, the cough test was found to show good agreement with urodynamic studies (UDS) in the detection of SUI [19]. Urethral mobility and PFM contraction strength can also be assessed. A focused neuro-urological examination should also be routinely undertaken.

3.1.1 Summary of evidence and recommendation for history taking and physical examination

Summary of evidence	LE
History taking including symptoms and co-morbidity and focused physical examination are essential parts of the evaluation of women with LUTS.	4

Recommendation	Strength rating
Take a complete medical history including symptoms and co-morbidity and perform a focused physical examination for evaluation of women with LUTS.	Strong

3.2 Patient questionnaires

This section includes symptom scores, symptom questionnaires/scales/indices, 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, should have been shown to be sensitive to change. The US Food and Drug Administration (FDA) published guidance for industry on PROM instruments (questionnaires) in 2009 [20].

Although many studies have investigated the validity and reliability of urinary symptom questionnaires and PROMs, most of these studies included mixed populations (men and women). This limits the extent to which results and conclusions from these studies can be applied to particular LUT syndromes in women. Some questionnaires (ICIQ-FLUTS, QUID, 3IQ, ICIQ-SF) have potential to discriminate UI types in women [21-23]. Others have been developed to measure symptoms and bother in OAB (OABQ-SF, B-SAQ) and other specific conditions. A newly developed patient assessment tool, the OAB- Bladder Assessment Tool (OAB-BAT), was found to be a valid and reliable OAB PROM that includes symptoms, bother, impacts and satisfaction with treatment [24]. A systematic review included 22 studies that assessed eleven case-finding tools for OAB. All tools were found to have good sensitivity and specificity for OAB or incontinence symptoms. The B-SAQ was the only tool in this SR to include screening for “red- flag” symptoms such as haematuria and pain, and it has also been validated in a primary care setting [25]. Some questionnaires are responsive to change and may be used to measure outcomes, although evidence for this is inconsistent [26, 27].

A SR including 73 studies assessed 27 specific and six generic instruments that measure quality of life (QoL) in women with UI. In this review, the incontinence questionnaire (IQoL) was found to be the most psychometrically robust disease-specific tool for use in English-speaking women with UI. It had the highest level of evidence for sufficient internal consistency, test-retest reliability, measurement error and hypothesis testing for construct validity. It is also the most translated instrument. Evidence on the performance of generic QoL tools for this population is limited [28]. There is no evidence to indicate whether use of QoL or condition-specific questionnaires has an impact on outcome of treatment.

Detailed description of the different urinary symptoms questionnaires and PROMs is beyond the scope of these guidelines. For more information, we recommend the 6th ICI review on PROM assessment [29]. To date, there is not one questionnaire that fulfils all requirements for assessment of women with LUTS. Clinicians must evaluate the tools that exist, for use alone or in combination, for assessment and monitoring of treatment outcome [30]. The questionnaires can be found on the following websites: www.iciq.net, https://eprovide.mapi-trust.org, www.pfizerpcoa.com, www.ncbi.nlm.nih.gov.

3.2.1 Summary of evidence and recommendation for patient questionnaires

Summary of evidence	LE
Validated condition-specific symptom scores assist in the screening for and categorisation of LUTS.	3
Validated symptom scores measure the severity of UI and LUTS.	3
Both condition-specific and general health status questionnaires measure current health status and change following treatment.	3
Patient questionnaires cannot replace a detailed patient consultation and should only be used as part of a complete medical history.	4

Recommendation	Strength rating
Use a validated and appropriate questionnaire as part of the standardised initial assessment and follow-up of female LUTS.	Strong

3.3 Bladder diaries

Measurement of the frequency and severity of LUTS is an important step in the evaluation and management of LUT dysfunction. Bladder diaries are a semi-objective method of quantifying symptoms, such as frequency of UI events, number of nocturia episodes, etc. They also quantify urodynamic variables, such as voided volume, 24-hour urine volume or nocturnal total urine volume.

Discrepancy between diary recordings and the patient rating of symptoms, e.g., frequency of UI, can be useful for patient counselling. Fluid intake and voided volume measurement can be used to support diagnoses and management planning, for example in OAB, and for identifying 24-hour or nocturnal polyuria. Diaries can also be used to monitor treatment response and are widely used in clinical trials. In patients with severe UI, a bladder diary is unlikely to accurately report 24-hour urine output.

Consensus terminology is now well-defined and widely accepted [1, 31]. However, the terms micturition diary, frequency/volume chart, bladder diary and voiding diary, have been used interchangeably for many years, but only bladder diaries include information on fluid intake, times of voiding, voided volumes, UI episodes, pad usage, degree of urgency and severity of UI recorded for at least 24 hours. When reviewing the evidence, all synonymous search terms have been included.

Two studies have demonstrated the reproducibility of diaries in both men and women [32, 33]. Other studies have shown the feasibility, reliability, and validity of the bladder diary [34, 35]. 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 [36, 37]. Another study found that keeping a bladder diary had a therapeutic benefit [38].

A number of observational studies have demonstrated a close correlation between data obtained from bladder diaries and standard symptom evaluation [39-42]. The optimum number of days required for bladder diaries appears to be based on a balance between accuracy and compliance [43, 44]. Diary durations between three and seven days are routinely reported in the literature.

3.3.1 Summary of evidence and recommendations for bladder diaries

Summary of evidence	LE
Bladder diaries of three to seven days duration are reliable tools for objective measurement of mean voided volume, day- and night-time frequency, urgency episodes, UI episode frequency fluid intake and pad usage.	2b
Bladder diaries are sensitive to change and are a reliable outcome measure.	2b

Recommendations	Strength rating
Ask patients with LUTS to complete a bladder diary as part of the standardised assessment of female LUTS.	Strong
Use a bladder diary with a duration of ≥ 3 days.	Strong

3.4 Urinalysis and urinary tract infection

Reagent strip (dipstick) urinalysis may indicate proteinuria, haematuria or glycosuria, or suggest UTI requiring further assessment. Please refer to the Urological Infections Guidelines for diagnosis and treatment of UTI [17].

Urine dipstick testing is a useful adjunct to clinical evaluation in patients in whom urinary symptoms are suspected to be due to UTI. Urinalysis negative for nitrite and leukocyte esterase may exclude bacteriuria in women with LUTS [45], and should be included, with urine culture when necessary, in the evaluation of all patients with LUTS. Urinary incontinence or worsening of LUTS may occur during UTI [46] and existing UI may worsen [47]. The rate and severity of UI were unchanged after eradication of asymptomatic bacteriuria in nursing home residents [48].

3.4.1 Summary of evidence and recommendations for urinalysis

Summary of evidence	LE
Urinalysis negative for nitrite and leukocyte esterase may exclude bacteriuria in women with LUTS.	3
Urinary incontinence may be a symptom during UTI, and LUTS may increase during UTI.	3
The presence of UTI worsens existing symptoms of UI.	3
Elderly nursing home patients with UI do not benefit from treatment of asymptomatic bacteriuria.	2

Recommendations	Strength rating
Perform urinalysis as a part of the initial assessment of patients with LUTS.	Strong
If an urinary tract infection is present with LUTS, reassess the patient after treatment.	Strong
Do not routinely treat asymptomatic bacteriuria in elderly patients with the aim of improving UI.	Strong

3.5 Post-void residual volume

Post-void residual (PVR) volume is the amount of urine that remains in the bladder after voiding. It is a measure of voiding efficiency, and results from a number of contributing factors. The detection of significant PVR volume is important because it may worsen symptoms and, may be associated with UTI, upper urinary tract (UUT) dilatation and renal insufficiency. Both bladder outlet obstruction (BOO) and/or detrusor underactivity (DU) can potentially contribute to the development of significant PVR volume. Post-void residual volume can be measured by catheterisation or ultrasound (US).

Most studies investigating PVR volume have assessed mixed populations including those with neurogenic UI, so results should be applied with caution to women with non-neurogenic LUTS. Studies investigating the best method of measuring PVR volume [48-53] conclude that US measurement of PVR volume is preferable to catheterisation due to its favourable risk–benefit profile.

The prevalence of significant PVR volume among patients with LUTS is uncertain, partly because of the lack of a standard definition of an abnormal PVR volume. Some authors have suggested that it is reasonable to consider a PVR volume > 100 mL to be significant, although many women may remain asymptomatic and hence it is imperative to consider the clinical context. There is no consensus on what constitutes a significant PVR volume in women [54-59], therefore the Panel prefers the use of bladder voiding efficiency (BVE) - the proportion of the total bladder volume that is voided by the patient. Bladder voiding efficiency can be calculated as a percentage: BVE = voided volume (VV)/(VV+PVR) × 100. This may be a more reliable parameter to evaluate poor voiding [46].

3.5.1 Summary of evidence and recommendations for post-void residual volume

Summary of evidence	LE
Women with lower urinary tract symptoms exhibit a higher PVR volume compared to asymptomatic women.	2

Recommendations	Strength rating
Measure post-void residual (PVR) volume in patients with LUTS during initial assessment.	Strong
Use ultrasound to measure PVR volume.	Strong
Monitor PVR volume in patients receiving treatments that may cause or worsen voiding dysfunction.	Strong
Provide bladder voiding efficiency as an additional parameter when measuring PVR volume.	Weak

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. The simplest form of urodynamic evaluation is uroflowmetry. The maximum flow rate (Q_{max}), the volume voided and the shape of the curve in addition to the PVR volume (see above) are the most important parameters to be assessed [29]. The bladder should be sufficiently full because of the volume dependency of Q_{max} [60, 61]. A minimum voided volume of 150 mL is advised in men, but there is little evidence to suggest a volume threshold in women. It is relevant to ask the patient whether or not the voiding is representative.

Invasive urodynamic tests are sometimes performed prior to invasive treatment of LUTS. These tests include multichannel cystometry and pressure–flow studies, ambulatory monitoring and video-urodynamics, and different tests of urethral function, such as urethral pressure profilometry. The International Continence Society (ICS) and the United Kingdom Continence Society (UKCS) provide standards to optimise urodynamic test performance and reporting [62, 63]. A characteristic of a good urodynamic study is that the patient's symptoms are replicated, recordings are checked for quality control, and results interpreted in the context of the clinical problem, remembering that there may be physiological variability within the same individual [62]. Non-invasive alternatives for measurement of detrusor pressure and BOO include transabdominal wall near-infrared spectroscopy and US detrusor wall thickness analysis, but as yet, these techniques have not been adopted into routine clinical practice [29].

Further condition-specific information regarding the role of urodynamic testing in OAB, SUI, BOO and UAB can be found in respective sections of these guidelines.

3.6.1 Variability

In common with most physiological tests there is variability in urodynamic results. This has consequences for the reproducibility, diagnostic accuracy, and predictive value of urodynamic testing. ICS Good Urodynamic Practice Guidelines state [62] that, at least in the case of cystometry and pressure–flow studies, one set of measurements suffices, but only if the patient's symptoms have been replicated but some studies contradict this [64, 65]. There is also conflicting evidence about the reproducibility of maximum urethral closure pressure (MUCP) measurement [64, 65]. Valsalva leak point pressure (VLPP) measurement is not standardised and there is minimal evidence about its reproducibility. No studies on the reproducibility of ambulatory monitoring in non-neurological patients have been published [29].

3.6.2 Diagnostic accuracy

Clinical diagnosis and cystometric findings sometimes do not correlate [66, 67] and asymptomatic women may have abnormalities on urodynamic testing. The diagnostic accuracy of urethral pressure profilometry [68] and urethral retro-resistance pressure measurement in SUI is poor [29]. Valsalva leak point pressure did not reliably assess UI severity in a cohort of women selected for surgical treatment of SUI [69]. Urethral pressure reflectometry may have greater diagnostic accuracy but its clinical role remains unclear [70]. Ambulatory urodynamics may detect unexpected physiological variance from normal more often than conventional cystometry does, but the clinical relevance of this is also uncertain [71, 72].

A pressure–flow study, that is, the simultaneous measurement of flow rate and detrusor pressure during voiding, can reveal whether a poor flow rate and PVR volume are due to BOO, DU or a combination of both. Also, it may provide information on the degree of pelvic floor relaxation and thus diagnose dysfunctional voiding. Several proposals to define BOO in women have been made. These definitions are based on detrusor pressure, either $P_{det}Q_{max}$ or the maximum value $P_{det.max}$, and the Q_{max} value, either during the pressure-flow study or during uroflowmetry. These measures are sometimes combined with the findings during fluoroscopic imaging (see Section 4.5.4.8) [73, 74]. Unlike the situation in men, there is no widely accepted threshold for BOO diagnosis in women. Bladder contraction strength parameters are derived from detrusor pressure and flow rate during a pressure-flow study or from stop tests [74], but again, validation is poor. Although these parameters estimate the strength of the contraction, they ignore its speed and persistence (see Section 4.4.3.2) [75]. A video-

urodynamic study can be useful to detect the site of obstructed voiding, which may be anatomical or functional [76]. Also, video-urodynamics may detect bladder diverticulum or gross reflux as a pressure-absorbing reservoir.

*3.6.3 **Predictive value***

Performing urodynamic evaluation is only useful if it leads to more effective clinical care and better outcomes. A Cochrane review of eight randomised controlled trials (RCTs) showed that use of urodynamic tests in women with UI increased the likelihood of prescribing drugs but did not increase the likelihood of undergoing surgery. However, there was no evidence that this altered the clinical outcome [77]. Most RCTs addressed the utility of urodynamic tests on SUI only, including women with uncomplicated SUI. A meta-analysis including four RCTs comparing surgical outcomes in women with self-reported SUI (or stress-predominant MUI) who were investigated via urodynamics with women who had office evaluation only, found that there was no difference in cure and complication rates [78]. In contrast, a large retrospective multicentre study found that only 36% of patients were defined as uncomplicated according to the definitions used in large RCTs [79]. The urodynamic observations were not consistent with the pre-urodynamic diagnosis in 1,276 out of 2,053 patients (62.2%). Voiding dysfunctions were urodynamically diagnosed in 394 patients (19.2%) and planned surgery was cancelled or modified in 304 of 1,582 patients (19.2%) in whom data were available, due to the urodynamic findings [80]. A large UK multi-centre RCT is underway designed to evaluate the effectiveness and cost-effectiveness of invasive urodynamic investigations in management of women with refractory OAB symptoms [81].

The predictive value of urethral function tests remains unclear. In observational studies, there was no consistent correlation between the results of these tests and subsequent success or failure of SUI surgery [40-42, 82]. The same was true in a secondary analysis of an RCT [83].

The presence of preoperative detrusor overactivity (DO) in women with stress-predominant MUI has been associated with postoperative UUI but did not predict overall treatment failure following mid-urethral sling (MUS) surgery or colposuspension [83]. The urodynamic diagnosis of DO has no predictive value for treatment response in studies on antimuscarinics, onabotulinumtoxinA and sacral nerve stimulation (SNS) in patients with OAB symptoms [84, 85]. Augmentation cystoplasty aims to abolish DO, improve bladder compliance, and increase functional bladder capacity but there is no evidence to guide whether or not preoperative urodynamics are predictive of outcome. Most clinicians would, however, consider preoperative urodynamics as essential prior to contemplating augmentation cystoplasty.

A pressure–flow study is capable of discriminating BOO from DU as a cause of voiding dysfunction. The predictive value of parameters derived from such a study for voiding dysfunction after a surgical procedure for SUI is, however, low. A low preoperative flow rate and a low detrusor voiding pressure have been shown to correlate with voiding dysfunction after a tension-free vaginal tape (TVT) and an autologous fascial sling procedure, respectively [86-88]. Bladder contraction strength parameters combining flow rate and detrusor pressure only poorly predicted voiding dysfunction after autologous fascial sling [89]. Post-hoc analysis of two high-quality surgical trials of TVT, Burch colposuspension and autologous fascial sling showed that no preoperative urodynamic parameter predicted postoperative voiding dysfunction in a selected population of women with low preoperative PVR volume [90, 91].

The Panel recognises that it may be valuable to use urodynamic test results to select the optimum management strategy; however, there is inconsistent evidence regarding the predictive value of such tests. When urodynamics and clinical assessment (i.e., by history and examination) are in disagreement, there needs to be a careful re-evaluation of the clinical symptoms and investigation results to ensure that the diagnosis is correct before invasive treatments are contemplated. Expert opinion recognises urodynamic testing as the most comprehensive analysis of LUT function and the primary aim of urodynamics includes reproduction of the patient's symptoms. The information one obtains from urodynamics may be very valuable to discuss and manage expectation regarding invasive treatment.

*3.6.4 **Summary of evidence and recommendations for urodynamics***

Summary of evidence	**LE**
Urodynamics provide comprehensive analysis of LUT function underlying different clinical conditions.	4
Most urodynamic parameters show variability within the same session and over time.	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 may be inconsistency between history and urodynamic results.	3
Urodynamic diagnosis of DO does not influence treatment outcomes in patients with OAB.	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 results of urethral function tests and subsequent success or failure of SUI surgery.	3
There is no consistent evidence that preoperative DO is associated with surgical failure of MUS in women.	3
The presence of preoperative DO may be associated with persistence of urgency postoperatively in women undergoing surgery for SUI.	3

Recommendations	**Strength rating**
Adhere to good urodynamic practice standards as described by the International Continence Society when performing urodynamics in patients with LUTS.	Strong
Do not routinely carry out urodynamics when offering treatment for uncomplicated stress urinary incontinence.	Strong
Do not routinely carry out urodynamics when offering first-line treatment to patients with uncomplicated overactive bladder symptoms.	Strong
Perform urodynamics if the findings may change the choice of invasive treatment.	Weak
Do not use urethral pressure profilometry or leak point pressure to grade severity of urinary incontinence.	Strong

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 provide objective evidence of response to treatment.

The clinical utility of pad tests in woman with UI has been assessed in three SR's [92-94]. One SR included eighteen studies and concluded that 1-hour pad test was more accurate but less reproducible when compared to the longer duration pad tests. 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 [95].

A pad test with a specific short graded exercise protocol also has diagnostic value but a negative test should be repeated with the degree of provocation increased [96]. The usefulness of pad tests in quantifying severity and predicting outcome of treatment is uncertain [92, 97, 98]. Pad tests are responsive to change following successful treatment [99]. Pad testing using a standardised bladder volume (50% of cystometric capacity) was suggested to allow for a more reliable assessment of UI in a small study of 25 women [100]. There is no evidence that one type of pad test is superior to another.

3.7.1 Summary of evidence and recommendations for pad testing

Summary of evidence	**LE**
A pad test can diagnose UI accurately.	2
Standardisation of bladder volume and degree of provocation improves reproducibility.	2
Twenty-four hours is sufficient duration for home-based testing balancing diagnostic accuracy and adherence.	1a
Change in leaked urine volume on pad tests can be used to measure treatment outcome.	2
Pad tests can be a useful tool in the research setting and are an optional investigation in clinical practice.	4

Recommendations	Strength rating
When a pad test is performed, use a standardised duration and activity protocol.	Strong
Use a pad test when quantification of urinary incontinence is required, especially to assess response to treatment.	Weak

3.8 Imaging

In clinical practice, imaging is used to understand the relationship between anatomy and function. Ultrasound and magnetic resonance imaging (MRI) have largely replaced X-ray imaging in the evaluation of the pelvic floor. Ultrasound is sometimes preferred to MRI because of its ability to produce three-dimensional (3D) and 4D (dynamic) images at lower cost and wider availability.

There is no need for UUT imaging unless a high-pressure bladder, severe POP or chronic urinary retention is suspected or diagnosed, or abnormal renal function tests are observed. In cases of suspected UI caused by an UUT anomaly or uretero-vaginal fistula, UUT imaging (urography, computed tomography [CT]) may be indicated [101].

*3.8.1 **Ultrasound***

Ultrasonography of the LUT plays a role in the differential diagnosis of women with LUTS and in cases presenting with haematuria.

Ultrasonography has been used in the evaluation of UI and pelvic floor since the 1980s. Different imaging approaches, such as abdominal, transvaginal, transrectal, perineal and transurethral are described. The bladder neck and urethra are easily visible, and measurements can be done at rest and during straining, coughing and pelvic floor contraction. The parameters assessed in the diagnosis of SUI, for example, include bladder neck mobility or descent, urethro-vesical angle, and urethral rotation [102, 103]. Ultrasonography can be used to assess PFMs and their function. Contraction of PFM results in displacement of pelvic structures that can easily be imaged on US. Integrity of the levator ani muscle can be determined by 3D transperineal US. Ultrasound may also provide information on the anatomical changes of the LUT and pelvic floor associated with persistence of symptoms post-treatment [104]. The specific role of US is discussed in the condition-specific sections of these guidelines where applicable.

*3.8.2 **Detrusor wall thickness***

As OAB syndrome is linked to DO, it has been hypothesised that frequent detrusor contractions may increase detrusor/bladder wall thickness (DWT/BWT). No consensus exists as to the relationship between OAB and increased BWT/DWT [105], and there is no evidence that BWT/DWT imaging improves management of OAB. There is no widely accepted standardised bladder volume for bladder wall thickness measurement.

In a retrospective study including 227 women with symptoms of voiding difficulty (hesitancy, intermittency, and poor stream), 74 (32.6%) were diagnosed with voiding dysfunction on the basis of free uroflowmetry and residual urine. While controlling for the effect of DO, the relationships between DWT and different parameters of voiding function in pressure–flow studies and free uroflowmetry were examined. The results indicated that DWT was not associated with any urodynamic parameters that may indicate BOO [106].

*3.8.3 **Magnetic resonance imaging***

There is a general consensus that MRI provides good global pelvic floor assessment, including POP, defecatory function and integrity of the pelvic floor support [107]. However, there is a large variation in MRI interpretation between observers [108] and little evidence to support its clinical usefulness in the management of LUTS/UI. There is no conclusive evidence that MRI evaluation of POP is more clinically useful than vaginal examination. Studies have assessed the use of imaging to assess the mechanism of MUS insertion for SUI. One study suggested that MUS placement decreased mobility of the mid-urethra but not of the bladder neck [109]. Following MUS, a wider gap between pubic symphysis and sling (assessed by imaging) has been shown to correlate with a lower chance of cure of SUI [110].

3.8.3.1 Summary of evidence and recommendation for imaging

Summary of evidence	LE
There is no consistent evidence that routine urinary tract imaging is useful in the evaluation or management of LUTS.	3
There is no consistent evidence that BWT/DWT measurement is useful in the management of OAB.	3

Recommendation	Strength rating
Do not routinely carry out imaging of the upper urinary tract or lower urinary tract as part of the assessment of LUTS.	Strong

3.9 Urinary biomarkers and microbiome

Interest in the role of urinary biomarkers for the diagnosis of LUT dysfunction has increased in recent years. Nerve growth factor (NGF), brain derived neurotrophic factor (BDNF), prostaglandin E2, adenosin triphosphate (ATP) and purinergic receptors (P2X) in bladder tissue have been studied as biomarkers for OAB. Serum beta natriuretic peptide (BNP), urinary 6-sulfaoxymelatonin and C-reactive protein (CRP), melatonin, vasopressin levels have been studied in relation to nocturia. For SUI, urinary IL 12-70, urinary (uNGF) N-telopeptide of type I collagen (NTx) and urinary microbiota have been studied. Currently, studies investigating urinary biomarkers are methodologically limited often due to failing to control for confounding variables and results are conflicting [111].

Another area of discovery is the role of urinary microbiota in identifying and differentiating various types of UI and other LUT disease in women. A SR described studies showing differences in the types and relative proportions of bacteria such as *Lactobacillus, Gardnerella, and Atopobium vaginae*, among women with different types of UI compared with healthy controls. Urinary microbiota has also been shown to differ depending on women's response to anticholinergic treatment response [112]. Further research is needed before the place of urine microbiota assessment in the clinical pathway for women with LUTS is fully defined.

Further information on the diagnostic efficacy of biomarkers in OAB can be found in Section 4.1.3.

3.9.1 ***Summary of evidence and recommendation for urinary biomarkers***

Summary of evidence	LE
There is insufficient evidence on the diagnostic accuracy and validity of urinary biomarkers for LUT disease in women.	3
Differences in the urinary microbiota have been found to be associated with different types of LUT dysfunction in women, including UI, and with different responses to treatment.	3

Recommendation	Strength rating
Do not routinely use urinary biomarkers or estimation of the urinary microbiota in the diagnosis and management of LUT disease in women.	Strong

4. DISEASE MANAGEMENT

4.1 Overactive bladder

4.1.1 ***Epidemiology, aetiology, pathophysiology***

Overactive bladder syndrome is defined by the ICS as "*urinary urgency, usually accompanied by frequency and nocturia, with or without UUI, in the absence of UTI or other obvious pathology*" [113]. Overactive bladder is a chronic condition that can have debilitating effects on QoL. The hallmark urodynamic feature is DO but the diagnosis of OAB is exclusively based on symptoms.

The EPidemiology of InContinence (EPIC) study [114] was a cross-sectional telephone survey of adults conducted in five countries and demonstrated an overall prevalence of OAB symptoms of 11.8% (10.8% in men and 12.8% in women).

Various theories have been proposed to explain the pathophysiology of OAB, mainly relating to imbalances in inhibitory and excitatory neural pathways to the bladder and the urethra or sensitivity of bladder muscle receptors. However, no definite identifiable causes have been established.

*4.1.2 **Classification***

Overactive bladder is generally classified into wet and dry, based on the presence or absence of associated UI.

*4.1.3 **Diagnostic evaluation***

Evaluation of symptoms of OAB follows the general pathway of evaluation of women with LUTS.

4.1.3.1 Bladder diaries

Diaries are particularly helpful in establishing and quantifying symptoms of frequency, urgency and UI, and may be valuable in assessing change over time or response to treatment. Several observational studies have demonstrated a close correlation between data obtained from bladder diaries and standard symptom evaluation [39-42]. The optimum number of days required for bladder diaries appears to be based on a balance between accuracy and compliance. Diary duration of three to seven days is routinely used in the literature. For further information, please review Section 3.3.

4.1.3.2 Urodynamics

Urodynamics is essential in establishing the presence of DO, but its absence does not preclude diagnosis of OAB, which is based on symptoms alone.

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 [77]. A sub-analysis of an RCT comparing fesoterodine to placebo [85] showed that the urodynamic diagnosis of DO was not predictive of treatment response.

4.1.3.3 Summary of evidence and recommendations regarding OAB diagnosis

Summary of evidence	**LE**
Bladder diaries of three to seven days' duration may be helpful in quantifying symptoms of OAB and assessing response to treatment.	3
Urodynamic diagnosis of DO does not influence treatment outcomes in patients with OAB.	1a

Recommendations	**Strength rating**
Request that patients complete at least a three-day bladder diary at initial evaluation for overactive bladder (OAB).	Strong
Do not routinely carry out urodynamics when offering first-line treatment to patients with uncomplicated OAB symptoms.	Strong

4.1.3.4 Urinary biomarkers

A SR and meta-analysis indicated that uNGF, BDNF to creatinine ratio and uNGF to creatinine ratio were all increased in female OAB patients compared to healthy controls, whereas no difference was found for the PGE2/Cr and ATP/Cr ratios [115]. The current data is inadequate to assess any other potential biomarkers, in the diagnosis or management of OAB in female patients.

*4.1.4 **Disease management***

4.1.4.1 Conservative management

In clinical practice, it has long been the convention that non-surgical therapies are recommended first because they usually carry the lowest risk of harm. While this remains true for non-pharmacological conservative treatments [e.g., pelvic floor muscle training (PFMT)], increasing concerns regarding the adverse events of some pharmacological treatments used to treat OAB (e.g., anticholinergic drugs), particularly regarding cognitive function, have emerged and patients should be fully counselled regarding this potential risk.

4.1.4.1.1 Addressing associated medical co-morbidities

Lower urinary tract symptoms, especially in elderly patients, are associated with multiple co-morbid conditions including:

- cardiac failure;
- chronic renal failure;
- diabetes;
- chronic obstructive pulmonary disease;
- neurological disease;
- general cognitive impairment;
- sleep disturbances, e.g., sleep apnoea;
- depression;
- metabolic syndrome.

If a change in co-morbidity or a new treatment for any associated co-morbidity has been linked to a deterioration in LUTS then this should be reviewed.

One study involving middle-aged women with type 1 diabetes mellitus showed that 10% had UUI. The study showed no correlation between early intensive insulin treatment of type 1 diabetes mellitus vs. conventional insulin treatment and the occurrence of UUI. The same study found no difference in the prevalence of UI in these patients later in their lives [116].

4.1.4.1.2 Adjustment of other medication

Although LUTS are listed as adverse effects of many drugs, this mainly derives from uncontrolled individual patient reports and post-marketing surveillance. Few controlled studies used the occurrence of LUTS as a primary outcome or were powered to assess the occurrence of statistically significant LUTS, or worsening rates against placebo. In most cases, it is therefore not possible to be sure that any drug causes OAB/LUTS.

A structured scoping review failed to identify any studies addressing whether adjustment of specific medications could alter existing symptoms of OAB.

4.1.4.1.2.1 Summary of evidence and recommendations for conservative management of OAB

Summary of evidence	**LE**
There is a lack of evidence that improving any associated co-morbid condition improves OAB.	3
There is little evidence that adjustment of specific medications for associated co morbid conditions can alter existing symptoms of OAB.	3

Recommendations	**Strength rating**
Take a history of current medication use from all patients with overactive bladder (OAB).	Strong
Review any new medication associated with the development or worsening of OAB symptoms.	Strong

4.1.4.1.3 Urinary containment

Urinary containment is important for people with OAB wet when active treatment does not cure the problem, is delayed, or when it is not available or possible. Some individuals may prefer urinary containment rather than active treatment with its associated risks. Containment includes the use of absorbent pads, urinary catheters, external collection devices and intravaginal devices. Detailed literature summaries can be found in the current International Consultation on Urological Diseases (ICUD) monograph [8] and in a European Association of Urology Nurses guidance document [117].

A SR of five RCTs comparing different types of pads found that pads filled with superabsorbent material were better than standard pads but evidence that disposable pads in preventing skin problems, were better than washable pads was inconsistent [118]. A series of three crossover RCTs examined performance of different pad designs for differing populations [119]. For women with light UI, disposable insert pads (within washable pouch pants) were most effective. In adults with moderate/severe UI, disposable pull-up pants were more effective for women.

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 [120]. A SR 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 [121].

Catheter-related bladder discomfort may be significant in women. Anticholinergics have been proposed to prevent or reduce this issue, but most of the evidence comes from clinical trials in the postoperative period, and the results are conflicting [122-125]. One retrospective study including 40 women (most of them neurogenic) with long-term bladder catheters found intravesical botulinum toxin injections helped to prevent bladder pain and discomfort and catheter bypass/leakage. Patients reported an improvement in QoL and a significant 83% reduction in urine leakage [126].

A Cochrane review summarising five trials comparing bladder washout policies in adults with indwelling urinary catheters found inconsistent evidence of benefit [127].

A Cochrane review summarising eight trials of whether antibiotic prophylaxis was beneficial for adults using clean intermittent self-catheterisation (CISC) or indwelling catheterisation found it reduced the incidence of symptomatic UTI but possible harms were not assessed [128]. A multicentre RCT from the UK involving patients practising CISC reported that prophylaxis reduced UTI incidence and was well-tolerated, but development of antibiotic resistance was a concern [129].

4.1.4.1.3.1 Summary of evidence and recommendations for urinary containment

Summary of evidence	**LE**
Pads are effective in containing urine.	1b
Antibiotic prophylaxis may help reduce incidence of UTI in patients who have an indwelling catheter or use CISC, but at the cost of increasing antimicrobial resistance.	1a

Recommendations	**Strength rating**
Ensure that women with overactive bladder (OAB) and/or their carers are informed regarding available treatment options before deciding on urinary containment alone.	Strong
Offer incontinence pads and/or containment devices for management of OAB wet, either for temporary symptom control or when other treatments are not planned.	Strong
Offer prophylactic antibiotics to patients on clean intermittent self-catheterisation or on indwelling catheter with recurrent urinary tract infection only after discussion regarding the risk of increasing antimicrobial resistance.	Strong

4.1.4.1.4 Lifestyle interventions

Examples of lifestyle factors that may be associated with UI include obesity, smoking, level of physical activity, regulation of bowel habit, and fluid intake. Modification of these factors may improve symptoms of OAB.

4.1.4.1.4.1 Caffeine intake

A scoping review of fourteen interventional and twelve observational studies reported that reduction in caffeine intake may reduce symptoms of urgency, but the certainty of evidence was low, with significant heterogeneity in study populations [130].

4.1.4.1.4.2 Fluid intake

Modification of fluid intake, particularly restriction, is a strategy commonly used by people with OAB. Any advice on fluid intake given by health care practitioners (HCPs) should be based on 24-hour fluid intake and urine output measurements as retrieved from the bladder diary. From a general health point of view, it should be advised that fluid intake should be sufficient to avoid thirst and that an abnormally low or high 24-hour urine output should be investigated. The few published RCTs involving women provide inconsistent evidence [131-133]. In most studies, the instructions for fluid intake were individualised and it was difficult to assess participant adherence. An RCT showed that a reduction in fluid intake by 25% improved symptoms in patients with OAB but did not improve UI [133]. Personalised fluid advice compared to generic advice made no difference to continence outcomes in people receiving anticholinergics for OAB, according to an RCT comparing drug

therapy alone to drug therapy with behavioural advice [134]. Patients should be warned of the potential consequences of fluid restriction such as worsening of constipation or development of UTI.

4.1.4.1.4.3 Weight loss

Being overweight or obese has been identified as a risk factor for LUTS in epidemiological studies [135, 136]. There is evidence that the prevalence of both UUI and SUI increases proportionately with body mass index (BMI) [137]. However, the evidence base largely relates to obesity and SUI rather than UUI and OAB. Therefore, no definite inference can be drawn between obesity and the prevalence of OAB.

4.1.4.1.4.4 Smoking cessation

Smoking cessation is a general public health measure and has been shown to be weakly associated with improving urgency, frequency, and UI [138, 139]. The effect of smoking cessation on LUTS was described as uncertain in a health technology assessment review [140].

4.1.4.1.4.5 Summary of evidence and recommendations for lifestyle interventions

Summary of evidence	**LE**
Reduction of caffeine intake may reduce symptoms of frequency and urgency.	2
Reduction in fluid intake by 25% may help improve symptoms of OAB but not UI.	1b
Personalised fluid intake advice when added to pharmacotherapy provides no additional benefit in patients with OAB.	2
Obesity is a risk factor for UI in women, but the relationship to other OAB symptoms remains unclear.	1b
There is weak evidence that smoking cessation improves symptoms of OAB.	3

Recommendations	**Strength rating**
Advise adults with OAB that reducing caffeine intake may improve symptoms of urgency and frequency, but not incontinence.	Strong
Review type and amount of fluid intake in patients with OAB.	Weak
Encourage overweight and obese adults with overactive bladder (OAB)/urinary incontinence to lose weight and maintain weight loss.	Strong
Provide smoking cessation strategies to patients with OAB who smoke.	Strong

4.1.4.1.5 Behavioural and physical therapies

Behavioural and physical therapies are often introduced as part of a package of care including lifestyle changes and patient education.

4.1.4.1.5.1 Prompted voiding and timed voiding

The term ‘prompted voiding’ implies that carers, rather than the patient, initiate the patient going to void with the aim of preventing or reducing UI. This applies largely to an assisted care setting. A SR (nine RCTs including mostly women with UI), comparing prompted voiding to standard care, suggested evidence of short-term benefit for management of UI [141].

Timed voiding is defined as fixed, predetermined, time intervals between voids and is applicable for those with or without cognitive impairment. A Cochrane review of timed voiding included four RCTs and found inconsistent improvement in continence compared with standard care in cognitively impaired adults [142].

4.1.4.1.5.2 Bladder training

Bladder training (BT) is a programme of patient education along with a scheduled voiding regimen with gradually increasing intervals. Specific goals are to correct faulty 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 OAB/UI is unclear.

A comparison of anticholinergic treatment with BT in one Cochrane review with seven RCTs showed inconsistent results in terms of cure rates but reported significantly more patients improved with anticholinergics [143]. The same review showed that the addition of anticholinergics to BT as part of behavioural modification resulted in more subjective improvement but no difference in objective outcomes.

Cognitive behavioural therapy involves the analysis of or change to a thought process related to the sensation of urgency or employment of a specified thought process during an episode of urgency. This includes mental distraction (the most common), relaxation and mindfulness practices. A SR on cognitive components of behavioural therapies for OAB concluded that they were neither well described nor rationalized. Behavioural therapy that includes cognitive component shows promise for OAB treatment, but its relative importance has not been well evaluated nor rigorously studied [144].

Another SR including 12 studies on the effect of cognitive behavioural therapy on women with UUI showed high level of evidence of its effectiveness on improving symptom severity and moderate level of evidence on QoL, psychological symptoms and patient satisfaction when compared with placebo. However, results were inconsistent with some studies showing no difference in objective parameters such as bladder capacity [145].

4.1.4.1.5.3 Pelvic floor muscle training

Pelvic floor muscle contraction can lead to simultaneous inhibition of urgency, detrusor contraction and incontinence [146]. Intensive and regular strength training of the PFMs over time increases both PFM contraction strength and endurance, and changes the morphology of the pelvic floor, which may yield more effective inhibition of the detrusor and help to stabilize the proximal urethra and improve urethral function. There is a lack of basic and mechanistic studies to confirm that change in pelvic floor morphology improves OAB symptoms.

A SR of eleven RCTs [147] including women with OAB compared the efficacy of PFMT vs. inactive control, usual care, other lifestyle modification or other intervention. Pelvic floor muscle training significantly reduced OAB symptoms (frequency and UUI) in five RCTs, while the remaining six reported no significant difference. Significant heterogeneity in protocols and outcomes was noted.

4.1.4.1.5.4 Electrical stimulation

The methods of delivery of electrical stimulation (ES) vary considerably. Electrical stimulation of the PFM can also be combined with other forms of conservative therapy, e.g., PFMT with and without biofeedback. Electrical stimulation is often used to assist women who cannot initiate contractions to identify their PFMs and in patients with OAB and UUI with the aim of inhibiting detrusor contraction. There is, however, a lack of basic and mechanistic studies to confirm this theory.

A SR of the effect of ES included 63 trials with 4,224 adults with OAB symptoms [148]. Moderate-quality evidence suggests that ES is more likely to improve OAB symptoms compared to sham control, no treatment, PFMT, and drug treatment. It was unclear if ES was more effective than placebo/sham for UUI. Insufficient or very low-quality evidence was available to determine the difference in the adverse event rates between ES and placebo/sham and the other active treatments.

A SR of nine studies compared the effects different techniques of electrical stimulation. Pooled analysis of three trials showed no difference between intravaginal stimulation and transcutaneous posterior tibial nerve stimulation (T-PTNS) in terms of urinary frequency, nocturia and QoL scores [149]. In the same review, pooled results from two studies which T-PTNS was compared with posterior tibial nerve stimulation (PTNS) showed no difference in urinary urgency, frequency and QoL scores [149].

4.1.4.1.5.4.1 Posterior tibial nerve stimulation

Electrical stimulation of the posterior tibial nerve delivers electrical stimuli to the sacral micturition centre via the S2–S4 nerve roots. Stimulation is percutaneous with a fine (34-G) needle, inserted just above the medial aspect of the ankle (P-PTNS). Transcutaneous stimulation is also available that delivers stimulation via surface electrodes that do not penetrate the skin. The optimal treatment schedule has not been determined, with daily and weekly regimens described [150].

A SR identified five RCTs (408 women) that compared PTNS with antimuscarinics. The PTNS techniques were significantly more effective than antimuscarinics in the reduction of UUI episodes with no significant difference in the reduction of overall symptoms score, frequency episodes or urgency episodes [11].

A SR of three studies comparing PTNS monotherapy with PTNS plus antimuscarinics, showed that the combination therapy added no statistically significant difference to PTNS monotherapy in the reduction of mean symptoms score, frequency episodes, nocturia episodes, or UUI episodes [11].

4.1.4.1.5.4.2 Percutaneous posterior tibial nerve stimulation

The reviewed studies included a SR, two twelve-week RCTs of P-PTNS compared with sham treatment [151-153], one RCT comparing PTNS to tolterodine, and a three-year extension trial utilising a maintenance protocol in patients with OAB [154, 155]. The results of studies of PTNS in women with OAB consistently showed significant and sustained improvement in symptoms from baseline, with similar improvement compared to treatment with tolterodine.

4.1.4.1.5.4.3 Transcutaneous posterior tibial nerve stimulation

A SR of thirteen trials (ten RCTs and three cohort studies) compared the efficacy of T-PTNS (duration four to twelve weeks) with sham treatment, anticholinergics, and exercise in treatment of adults with OAB symptoms [156]. Of note, the populations were adult women and men, and some studies included patients with neurogenic OAB. Meta-analysis was possible in two RCTs comparing T-PTNS with sham treatment and revealed mean reduction in total International Consultation on Incontinence modular questionnaire (ICIQ) Urinary Incontinence Short Form (ICIQ-UI-SF) associated with T-PTNS of −3.79 points.

A small RCT compared T-PTNS plus standard treatment (PFMT and BT) with PFMT and BT alone in older women [157]. Women in the T-TPNS group were more likely to achieve improvement.

A small RCT compared BT alone, BT plus P-PTNS and BT plus T-PTNS in women with idiopathic OAB. Both P-PTNS and T-PTNS were more effective than BT alone. These two tibial nerve stimulation methods had similar clinical efficacy but with slight differences: T-PTNS had shorter preparation time, less discomfort level and higher patient satisfaction than P-PTNS [158].

4.1.4.1.5.5 Acupuncture

A SR with meta-analysis of ten RCTs including 794 patients (590 women) reported that acupuncture might have an effect in reducing OAB symptoms compared to sham treatment [159]. The studies were of low quality and compared electro-acupuncture vs. sham acupuncture, or electro-acupuncture plus tolterodine vs. tolterodine alone.

4.1.4.1.5.6 Summary of evidence and recommendations for behavioural and physical therapies

Summary of evidence	**LE**
Prompted voiding, either alone or as part of a behavioural modification programme, improves continence in elderly, care-dependent, people in the short-term.	1b
Bladder training is effective for improvement of UUI in women, but efficacy appears to be lower than that of pharmacotherapy.	1b
Pelvic floor muscle training may improve symptoms of frequency of OAB in women.	1b
Electrical stimulation may improve symptoms of OAB in some women, but the type and mode of delivery of ES remains variable and poorly standardised.	1a
Posterior tibial nerve stimulation is more effective than antimuscarinics in reducing UUI episodes but with no difference in improving other OAB symptoms.	1a
A maintenance programme of P-PTNS has been shown to be effective for up to 3 years.	2a
Transcutaneous-PTNS appears to be effective in reducing OAB symptom compared to sham treatment.	1a
Transcutaneous -PTNS is not inferior to percutaneous -PTNS with regard to improvement in urinary urgency, frequency, and QoL scores.	1a

Recommendations	**Strength rating**
Offer prompted voiding to adults with overactive bladder (OAB) who are cognitively impaired.	Strong
Offer bladder training as a first-line therapy to adults with OAB/urge urinary incontinence (UUI).	Strong
Ensure that pelvic floor muscle training programmes are as intensive as possible.	Strong
Consider posterior tibial nerve stimulation as an option for symptomatic improvement of OAB/UUI.	Strong

4.1.4.2 Pharmacological management

4.1.4.2.1 Anticholinergic drugs

Anticholinergic (antimuscarinic) drugs are currently the mainstay of treatment for OAB. Different agents vary in their pharmacological profiles, such as muscarinic receptor affinity and other modes of action and in their pharmacokinetic properties, such as lipid solubility and half-life.

The Panel SR identified twelve studies (11,179 women) comparing antimuscarinics with placebo. Antimuscarinics were significantly more effective than placebo in improving mean symptom score on OABQ, reducing daily frequency episodes, reducing daily urgency episodes and UUI episodes, and increasing bladder functional capacity [11].

The SR established that antimuscarinics caused significantly higher adverse events than placebo including dry mouth, cognitive impairment, UTI and constipation [11].

Immediate-release (IR) anticholinergic preparations provide maximum dosage flexibility, including an off-label on-demand use. Immediate-release drugs have a greater risk of adverse effects than extended release (ER) formulations because of differing pharmacokinetics. A transdermal delivery system and gel developed for oxybutynin provide alternative formulations. On balance, IR formulations tend to be associated with more adverse effects compared to ER formulations [160].

A network meta-analysis of 128 RCTs including both genders comparing anticholinergics with placebo or other anticholinergics revealed that all anticholinergics, except imidafenacin, showed reasonable cure or improvement rates for OAB symptoms in both sexes [161]. Differences across the drugs in terms of alteration in symptoms were small.

Cure of UUI is deemed to be the most important outcome measure. Table 1 shows a summary of the findings from a SR of RCTs including only women [162]. All agents showed superiority compared to placebo, but the absolute size of the effect was small.

Table 1: Summary of cure and discontinuation rates of anticholinergic drugs from RCTs [163]

Drug	**No. of studies**	**No. of patients**	**RR (95% CI) (of curing UI)**	**NNT (95% CI) (to achieve one cure of UI)**
Cure of incontinence				
Fesoterodine	2	2,465	1.3 (1.1–1.5)	8 (5–17)
Oxybutynin (includes IR)	4	992	1.7 (1.3–2.1)	9 (6–16)
Propiverine (includes IR)	2	691	1.4 (1.2–1.7)	6 (4–12)
Solifenacin	5	304	1.5 (1.4–1.6)	9 (6–17)
Tolterodine (includes IR)	4	3,404	1.2 (1.1–1.4)	12 (8–25)
Trospium (includes IR)	4	2,677	1.7 (1.5–2.0)	9 (7–12)
Discontinuation due to adverse events				
			RR (95% CI) (of discontinuation)	**NNT (95% CI) (for one discontinuation)**
Darifenacin	7	3,138	1.2 (0.8–1.8)	
Fesoterodine	4	4,433	2.0 (1.3–3.1)	33 (18–102)
Oxybutynin (includes IR)	5	1,483	1.7 (1.1–2.5)	16 (8–86)
Propiverine (includes IR)	2	1,401	2.6 (1.4–5)	29 (16–77)
Solifenacin	7	9,080	1.3 (1.1–1.7)	78 (39–823)
Tolterodine (includes IR)	10	4,466	1.0 (0.6–1.7)	
Trospium (includes IR)	6	3,936	1.5 (1.1–1.9)	56 (30–228)

CI = confidence interval; IR = immediate release; NNT = number to treat; RR = relative risk; UI = urinary incontinence.

The cure rates for darifenacin were not included in the US Agency for Healthcare Research and Quality (AHRQ) review. Continence rates were 29–33% for darifenacin compared to 17–18% for placebo [163]. Transdermal oxybutynin showed a significant improvement compared with placebo and other oral formulations in the number of incontinence episodes and micturitions per day but cure of UI was not reported as an outcome [163]. Oxybutynin topical gel was superior to placebo for improvement of UUI, with a higher proportion of participants being cured [163, 164].

4.1.4.2.1.1 Comparison of different anticholinergic agents

Head-to-head comparison trials of the efficacy and adverse effects of different anticholinergic agents are of interest for decision-making.

Both a network meta-analysis and a SR revealed no superior anticholinergic preparation for cure or improvement [161, 165]. There were no clinically significant differences between anticholinergics for voiding and UI outcomes. No single anticholinergic agent improved QoL more than another [165].

Conflicting results were reported from another network meta-analysis of 53 RCTs that compared the efficacy and tolerability of solifenacin 5 mg/day with other oral anticholinergics in the treatment of adults with OAB symptoms [166]. Solifenacin 5 mg/day was significantly more effective than tolterodine 4 mg/day for reducing UUI episodes, but significantly less effective than solifenacin 10 mg/day for reducing micturition episodes. Solifenacin 5 mg/day showed significantly lower risk of dry mouth compared with other anticholinergics but no significant differences for the risk of blurred vision or constipation.

A further network meta-analysis with 128 RCTs including both genders showed that all anticholinergics were worse than placebo in terms of dry mouth with transdermal oxybutynin having the smallest difference [161].

Dry mouth is the most prevalent reported adverse effect. Extended-release formulations are associated with lower rates of dry mouth than IR preparations [165, 167]. Oxybutynin IR shows higher rates of dry mouth than tolterodine IR and trospium IR but lower rates of dry mouth than darifenacin, 15 mg daily [165, 167]. Overall, oxybutynin ER causes higher rates of dry mouth than tolterodine ER does, although the incidence of moderate or severe dry mouth is similar. Transdermal oxybutynin has a lower rate of dry mouth than oxybutynin IR and tolterodine ER but an overall higher rate of withdrawal due to adverse skin reactions [165]. Solifenacin 10 mg daily has higher rates of dry mouth than tolterodine ER [165]. Fesoterodine 8 mg daily has a higher rate of dry mouth than tolterodine 4 mg daily [168-170]. Similar discontinuation rates have been observed, irrespective of differences in the occurrence of dry mouth.

It is notable that nearly all the primary studies in this category were industry sponsored. In general, these studies have been designed to achieve regulatory approval. Upward dose titration is often included in the protocol for the experimental arm but not for the comparator arm. They have short treatment durations (twelve weeks) and a primary outcome of a change in OAB symptoms rather than a cure of, or an improvement in, UUI, which were generally analysed as secondary outcomes. The clinical utility of these trials in real-life practice is therefore debatable. Most trials were of low or moderate quality [165].

4.1.4.2.1.2 Anticholinergic drugs versus conservative treatment

More than 100 RCTs and high-quality reviews are available detailing relative efficacy of anticholinergic drugs and conservative treatment strategies [143, 165, 171-174]. Most of these were independent studies. The main focus of the reviews was to compare the different drugs used to treat UUI. A U.S. health technology assessment [172] found that the vast majority of trials were of a low or moderate quality.

4.1.4.2.1.2.1 Anticholinergic drugs in combination with other conservative treatment versus anticholinergic drugs alone

The combination of BT and solifenacin in female patients with OAB confers no additional benefit in terms of continence compared with solifenacin monotherapy [175]. A recent Cochrane review on the benefit of adding PFMT to other active treatments of UI in women showed insufficient evidence of any benefit in adding PFMT to drug treatment [176].

One SR identified thirteen RCTs comparing outcomes of antimuscarinic mono-therapy with combinations of antimuscarinics plus adjunct treatments including topical oestrogen, pregabalin, Stroller neurostimulation (SANS), PFMT, and behavioural therapy. Antimuscarinics alone were less effective than a combination of antimuscarinics plus another treatment modality in reducing urgency episodes, UUI episodes, frequency and nocturia episodes and in improving the mean symptoms score but no significant differences were found in rates of dry mouth, constipation or voiding dysfunction [11].

4.1.4.2.1.3 Anticholinergic drugs: adherence and persistence

Most studies on anticholinergic medication are short term (twelve weeks). Adherence in clinical trials is considered to be higher than in clinical practice [177]. Discontinuation rates were high for tolterodine at twelve months, and particularly high (68–95%) for oxybutynin. Two open-label extensions of RCTs of fesoterodine 8 mg showed adherence rates at two years of 49–84% [178, 179].

A longitudinal disease analyser database study has indicated an increasing discontinuation rate, following treatment with anticholinergics, from 74.8% at one year to 87% at three years [180].

Several of the RCTs tried to identify the factors associated with low/lower adherence or persistence of anticholinergics. These were identified as:

- low level of efficacy (41.3%);
- adverse events (22.4%);
- cost (18.7%), although higher adherence rates were observed when drugs were provided at no cost to patients [181].

Other factors associated with poor adherence included:

- immediate release formulations (lower persistence compared with ER formulations);
- age (lower persistence among younger adults);
- unrealistic expectations of treatment;
- gender distribution (better adherence/persistence in female patients);
- ethnic group (African–Americans and other ethnic minorities are more likely to discontinue or switch treatment).

4.1.4.2.1.4 Summary of evidence and recommendations for anticholinergic drugs

Summary of evidence	**LE**
Anticholinergic drugs are effective in improving OAB symptoms, decreasing UUI episodes, decreasing daily urgency and frequency episodes and increasing mean voided volumes, compared with placebo.	1a
Anticholinergic drugs caused higher adverse events than placebo including dry mouth, cognitive impairment, and constipation.	1a
Once daily (ER) formulations are associated with lower rates of adverse events compared to IR preparations.	1b
Transdermal oxybutynin is associated with lower rates of dry mouth than oral anticholinergic drugs but has a higher rate of withdrawal due to skin reactions.	1b
Higher doses of anticholinergic drugs are more effective to improve OAB symptoms but exhibit a higher risk of adverse effects.	1a
No anticholinergic drug is clearly superior to another for cure or improvement of OAB/UUI.	1a
The combination of antimuscarinics plus another treatment modality was more effective than antimuscarinics alone in improving OAB.	1a
Adherence to anticholinergic treatment is low and decreases over time because of lack of efficacy, adverse events and/or cost.	2a
Most patients will stop anticholinergic agents within the first three months.	2a

Recommendations	**Strength rating**
Offer anticholinergic drugs to woman with overactive bladder (OAB) who fail conservative treatment.	Strong
Consider extended-release formulations of anticholinergic drugs whenever possible.	Strong
If an anticholinergic treatment proves ineffective, consider dose escalation, offering an alternative anticholinergic formulation, or the use of mirabegron (alone or in combination with an anticholinergic).	Strong
Encourage early review (of efficacy and adverse effects) of patients on anticholinergic medication for OAB.	Strong

4.1.4.2.2 Beta-3 Agonists

Beta-3 adrenoceptors are the predominant beta receptors expressed on detrusor smooth muscle cells and their stimulation is thought to induce detrusor relaxation. Mirabegron was the first clinically available beta-3 agonist. Vibegron is another beta-3 agonist commercially available in some countries.

Mirabegron has undergone evaluation in industry-sponsored phase II and III trials [182-185]. Three SRs assessing the clinical effectiveness of mirabegron [182, 183, 186] reported that mirabegron at doses of 25, 50 and 100 mg results in significantly greater reduction in UI episodes, urgency episodes and micturition frequency than placebo, with no difference in the rate of common adverse events [183]. The dry rates in most of these trials are 35–40% for placebo and 43–50% for mirabegron. In all trials the significant differences were consistent only for improvement but not for cure of UI. Similar improvements in the frequency of UI episodes and micturition frequency were found whether or not patients had previously tried anticholinergic agents.

The most common adverse events in the mirabegron groups were hypertension (7.3%), nasopharyngitis (3.4%) and UTI (3%), with the overall rate similar to that with placebo [182, 185, 187].

A SR with meta-analysis of data pooled from three RCTs comparing vibegron (75 mg or 100 mg) with placebo in 2,120 patients with OAB revealed significant improvement of urgency episodes and UUI episodes and mean voided volume associated with vibegron [188]. The review also reported that vibegron showed a favourable safety profile. Another SR that included three high-quality RCTs compared vibegron with anticholinergic monotherapy (imidafenacin and tolterodine) concluding similar efficacy in terms of improvements in mean number of micturitions, urgency and UUI, but with less dry mouth [189].

4.1.4.2.2.1 Beta-3 agonists versus anticholinergics

One SR [190] assessed the outcomes of mirabegron in women with OAB. It included seven RCTs, three non-randomised comparative studies and eleven observational studies. The review reported no statistical difference between mirabegron and anticholinergics in decreasing OAB symptoms on voiding diaries and symptom questionnaires on short-term follow-up (up to twelve weeks). However, at one year follow-up, there was a statistically significant decrease in OAB symptoms in favour of mirabegron.

Another SR identified four studies on 371 women that compared beta-3 agonists with antimuscarinics. Pooled analysis for the studies showed that beta-3 agonists were significantly more effective than antimuscarinics in reducing nocturia episodes. No significant differences were found between antimuscarinics and beta-3 agonists in reduction of mean symptoms score, urgency episodes, frequency episodes, UUI episodes, or voided volumes [11].

Antimuscarinics caused higher rates of dry mouth than beta-3 agonists, but no significant difference was found in constipation rates [11].

Post hoc analyses of RCTs showed that clinical improvement in OAB severity translates into improvement in HRQoL and efficacy is maintained in patients with more severe UI [191, 192]. No risk of QTc prolongation [193] and no raised intraocular pressure [194] were observed up to the 100 mg dose; however, patients with uncontrolled hypertension or cardiac arrhythmia were excluded from these trials. There is no significant difference in the rate of adverse effects at different doses of mirabegron [187].

Equivalent adherence was observed for tolterodine and mirabegron at twelve months (5.5% and 3.6%), although the incidence of dry mouth was significantly higher in the tolterodine group [187]. In mirabegron-treated patients, improvement in objective outcome measures correlates directly with clinically relevant PROMs (Overactive Bladder questionnaire and Patient Perception of Bladder Condition) [191, 195]. Data from a large Canadian Private Drug Plan database suggest a higher adherence rate for mirabegron compared to anticholinergics [196].

An RCT in patients who had inadequate response to solifenacin monotherapy 5 mg demonstrated that combination treatment with mirabegron 50 mg had a higher chance of achieving clinically meaningful improvement in UI as compared to dose escalation of solifenacin [197].

4.1.4.2.2.2 Summary of evidence and recommendation for Beta-3 agonists

Summary of evidence	LE
Mirabegron and vibegron are better than placebo for improvement of OAB/UUI symptoms.	1a
Adverse event rates with mirabegron and vibegron are similar to those of placebo.	1a
Beta-3 agonists are as effective as antimuscarinics in the management of OAB but with lower dry mouth rates.	1a
Patients inadequately treated with solifenacin 5 mg may benefit more from the addition of mirabegron rather than dose escalation of solifenacin.	1b

Recommendations	Strength rating
Offer beta-3 agonists as an alternative to anticholinergics to women with OAB who fail conservative treatment.	Strong
Offer mirabegron as an additional therapy in patients who are inadequately treated with solifenacin 5 mg.	Weak

4.1.4.2.3 Anticholinergics and beta-3 agonists: elderly patients and cognition

Systematic reviews have included sections on the efficacy and safety of anticholinergics in elderly patients [163, 165] but an older SR found inconclusive evidence of the impact of anticholinergics on cognition [198].

Two more recent longitudinal cohort studies in patients using anticholinergic drugs showed deterioration in cognitive function, alteration in central nervous system metabolism and an association with brain atrophy [199, 200]. As most of the study periods are short (four to twelve weeks), the long-term impact of anticholinergic agents specifically approved for OAB treatment on specific patient cohorts are poorly understood [201-204].

- *Oxybutynin:* There is evidence that oxybutynin IR may cause/worsen cognitive dysfunction in adults [201, 203, 205, 206]. Whilst short-term trials showed no effect on recent memory or other cognitive functions [206], prospective studies showed cumulative cognitive deterioration associated with prolonged use (mean follow-up, 7.3 years) of anticholinergic medication including oxybutynin [199]. Another prospective cohort study including 376 nursing home residents aged 65 and older taking oxybutynin and tolterodine showed a decline in activity of daily living after a median follow-up of 141 days, in spite of concomitant treatment with cholinesterase inhibitors [207].

- *Solifenacin:* One pooled analysis [208] showed that solifenacin did not increase cognitive impairment in elderly patients. No age-related differences in the pharmacokinetics of solifenacin in different age groups were found, although more frequent adverse events in patients aged > 80 years were observed. No cognitive effect on healthy elderly volunteers was shown [209]. In a sub-analysis of a large trial, solifenacin 5–10 mg improved symptoms and QoL in people aged ≥ 75 years who had not responded to tolterodine [210]. In patients with mild cognitive impairment, aged ≥ 65 years, solifenacin showed no difference in efficacy between age groups and a lower incidence of most adverse effects compared to oxybutynin IR [206, 211].

- *Tolterodine:* No change in efficacy or adverse effects related to age has been reported, although a higher discontinuation rate was found for both tolterodine and placebo in elderly patients [201]. Two RCTs in elderly patients found similar efficacy and adverse effect profile to those in younger patients [212-215]. *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 [216]. Duration of the RCTs was short (twelve weeks).

- *Darifenacin:* Two RCTs in the elderly population (one in patients with UUI and the other in volunteers) concluded that, compared with placebo, darifenacin was effective with no risk of cognitive change, measured as memory scanning tests [217, 218]. Another study on darifenacin and oxybutynin ER in elderly people concluded that the two agents had similar efficacy, but that cognitive function was more often affected in the oxybutynin ER arm [203].

- *Trospium chloride:* Trospium does not appear to cross the blood–brain barrier in healthy individuals due to its molecular characteristics (quaternary amine structure and hydrophilic properties). Two studies in healthy volunteers using electroencephalography showed no effect from trospium, while tolterodine caused occasional changes and oxybutynin caused consistent changes [219, 220]. No evidence as to the comparative efficacy and adverse effect profiles of trospium in different age groups are available. However, there is some evidence that trospium does not impair cognitive function in Alzheimer's disease patients if combined with cholinesterase inhibitors over a six month period [204], or in non-cognitively impaired patients over shorter periods (twelve weeks) [221] and that it is effective compared to placebo in the elderly [222].

- *Fesoterodine:* Pooled analyses of the RCTs of fesoterodine confirmed the efficacy of 8 mg but not 4 mg dose in patients aged > 75 years [178]. Adherence was lower in patients aged > 75 years but effects on mental status were not reported [170, 178, 223]. A more recent RCT showed efficacy of fesoterodine in vulnerable elderly people with no differences in cognitive function at twelve weeks [224].

- *Mirabegron:* Analysis of pooled data from three RCTs showed efficacy and safety of mirabegron in elderly patients [225].

4.1.4.2.3.1 Applicability of evidence to the general elderly population

It is not clear how much the data from pooled and subgroup analyses from large RCTs can be extrapolated to a general ageing population. Community-based studies of the prevalence of anticholinergic adverse effects may be the most helpful [226]. When starting anticholinergics in elderly patients, mental function should be assessed and monitored [227]. No consensus exists as to the best mental function test to detect changes in cognition [207, 228].

4.1.4.2.3.2 Anticholinergic burden

Several drugs have anticholinergic effects and, if another anticholinergic drug is prescribed, possible cumulative effects on cognition should be considered. Lists of drugs with anticholinergic properties are available from several sources [229].

Two SRs of largely retrospective cohort studies showed a consistent association between long-term anticholinergic use and cognitive dysfunction [230, 231]. Longitudinal studies in older people over two to four years have found increased rates of cognitive decline in patients on anticholinergics or drugs with anticholinergic effects [199, 200, 232, 233]. It is unclear whether there is a direct correlation between cognitive dysfunction caused by medication and the long-term risk of development of dementia.

4.1.4.2.3.3 Summary of evidence and additional recommendations for use of anticholinergic and beta-3 agonists in elderly patients

Summary of evidence	**LE**
Anticholinergic drugs are effective in elderly women suffering from OAB/UUI.	1b
Mirabegron has been shown to be efficacious and safe in elderly women suffering from OAB.	1b
In older women the cognitive impact of drugs with anticholinergic effects is cumulative and increases with length of exposure.	2
Oxybutynin may worsen cognitive function in elderly women.	2
Darifenacin, fesoterodine, solifenacin and trospium have not been shown to cause cognitive dysfunction in elderly women in short-term studies.	1b

Recommendations	**Strength rating**
Long-term anticholinergic treatment should be used with caution in elderly women, especially those who are at risk of, or have pre-existing cognitive dysfunction.	Strong
Assess anticholinergic burden and associated co-morbidity in women being considered for anticholinergic therapy for overactive bladder syndrome.	Weak

4.1.4.2.4 Oestrogens

Oestrogen treatment for UI has been tested using oral, transdermal, and vaginal routes of administration. Vaginal (local) treatment is primarily used to treat symptoms of vaginal atrophy in postmenopausal women. Available evidence is related mainly to SUI, and although some reviews include participants with UUI, it is difficult to generalise the results to women with predominantly OAB/UUI.

The association of LUTS with genitourinary syndrome of menopause (GSM) should be considered [234]. Genitourinary syndrome of menopause is a new term that describes various menopausal symptoms and signs associated with physical changes of the vulva, vagina and LUT. These include mucosal pallor/erythema, loss of vaginal rugae, tissue fragility/fissures, vaginal petechiae, urethral mucosal prolapse, introital retraction and vaginal dryness. There is evidence from a SR to suggest benefit from vaginal oestrogen therapy in GSM [235]. All vaginal oestrogens demonstrated superiority in objective and subjective end points of GSM compared with placebo. Only some trials demonstrated superiority vs. placebo in urogenital symptoms (UI, recurrent UTI, urgency, and frequency). No significant difference was observed between various doses and dosage forms of vaginal oestrogen products. Vaginal oestrogen showed superiority over vaginal lubricants and moisturisers for the improvement of objective clinical end points of vulvovaginal atrophy but not for subjective end points [235].

Available evidence suggests that vaginal treatment with oestradiol and oestriol is not associated with increased risk of thromboembolism, endometrial hypertrophy, and breast cancer that is seen with systemic administration [236-238].

4.1.4.2.4.1 Summary of evidence and recommendation for oestrogen therapy

Summary of evidence	**LE**
Vaginal oestrogen therapy may improve symptoms associated with GSM, of which OAB may be a component.	1a

Recommendation	**Strength rating**
Offer vaginal oestrogen therapy to women with LUTS and associated symptoms of genitourinary syndrome of menopause.	Weak

4.1.4.2.5 Placebo and nocebo

Placebo has a clear effect on the improvement of OAB signs and symptoms, and the overall placebo responses in various outcomes studied are statistically significant and, for some of the outcomes, possibly clinically significant. A recent SR including 57 studies with 12,901 patients showed a standardised mean difference of -0.45 for daily micturition episodes, -0.33 for daily nocturia episodes, -0.46 for UUI episodes, -0.50 for daily urgency episodes, -0.51 for daily incontinence episodes, and 0.25 for volume voided per micturition [239]. The same group published a SR with meta-analysis of data retrieved from 57 RCTs on the nocebo effect of pharmacotherapy in patients with OAB (up to 80% females). They reported dry mouth as the most common reported adverse event with mean rate of 4.9%, followed by constipation 2.6%. The authors concluded that HCPs should appreciate the possible positive and negative patient expectation regarding pharmacotherapy for OAB in order to optimise the individual outcomes [240]. The placebo response seems to be non-negligible in OAB, supporting the requirement for placebo control in RCTs.

4.1.4.3 Surgical management

4.1.4.3.1 Bladder wall injection of botulinum toxin A

OnabotulinumtoxinA (onabotA; BOTOX®) 100 U is licenced in Europe to treat OAB with persistent or refractory UUI in adults of both sexes [241, 242]. Surgeons should be aware that other doses of onabotA and other formulations of botulinum toxin A, abobotulinumtoxin A and incobotulinumtoxin A, are not licensed for use in OAB/UUI. Doses for onabotA are not transposable to the other brands of onabotulinumtoxinA. The continued efficacy of repeat injections is usual, but discontinuation rates may be high [243, 244]. The most important adverse events related to onabotA 100 U injection detected in the regulatory trials were UTI and an increase in PVR volume that may require CISC [245].

A SR included ten studies on 2,055 patients comparing intravesical onabotA injection with placebo. OnabotulinumtoxinA was more effective than placebo in improvement of mean symptoms score, reduction of mean urgency episodes, mean UUI episodes, mean frequency episodes, mean nocturia episodes [11]. No statistically significant difference was found between onabotA and placebo in change of mean voided volumes or maximum cystometric capacity.

OnabotulinumtoxinA was associated with significantly higher rates of voiding dysfunction compared to placebo at both 100 unit dose and 200 unit dose, and significantly higher rates of UTI both at 100-unit dose and 200-unit dose.

A Cochrane review reported no significant difference in PVR volume between the onabotA and placebo groups [246].

Quality of life was substantially improved in the onabotA arm, as shown by the > 2.5 times improvement in Incontinence Quality of Life Questionnaire (I-QOL) scores compared to baseline. Cohort studies have shown the effectiveness of bladder wall injections of onabotA in elderly and frail elderly people [247], although the success rate might be lower and the PVR volume (> 150 mL) higher in this group.

The median time to request retreatment in the pooled analysis of the two RCTs was 24 weeks [242, 245]. Follow-up over 3.5 years showed consistent or increasing duration of effect for each subsequent treatment, with a median of 7.5 months. Considerable differences were noted in patients' outcomes on secondary analysis [248].

Two RCTs on 545 patients compared onabotA injections with antimuscarinics. OnabotulinumtoxinA was significantly more effective in curing UUI, but no significant difference was noted in the reduction of mean UUI episodes. However, it was associated with significantly higher rates of voiding dysfunction than antimuscarinics, and UTIs [11].

Identification of DO in urodynamics does not appear to influence the outcome of onabotnA injections in patients with UUI [249].

4.1.4.3.1.1 Summary of evidence and recommendations for bladder wall injection of onabotulinumtoxinA

Summary of evidence	**LE**
A single treatment session of onabotA (100 U) injected in the bladder wall is more effective than placebo at curing and improving UUI/OAB symptoms and improving QoL.	1a
There is no evidence that repeated injections of onabotA have reduced efficacy, but discontinuation rates are high.	2a
There is a risk of voiding dysfunction, increased PVR volume and UTI with onabotA injections.	1a
The risk of bacteriuria after onabotA (100 U) injection is high but the clinical significance of this remains uncertain.	1b
OnabotulinumtoxinA is more effective in curing UUI but similarly effective in reducing mean UUI episodes compared with antimuscarinics.	1a
OnabotulinumtoxinA is associated with higher rates of voiding dysfunction than antimuscarinics.	1a

Recommendations	**Strength rating**
Offer bladder wall injections of onabotulinumtoxinA (100 U) to patients with OAB/UUI refractory to conservative therapy or drug treatment.	Strong
Warn patients of the limited duration of response, risk of UTI and possible prolonged need for clean intermittent self-catheterisation prior to offering treatment with onabotulinumtoxinA.	Strong

4.1.4.3.2 Sacral nerve stimulation

Sacral nerve stimulation (SNS) involves placing electrodes adjacent to the sacral nerve roots and delivering an electric current to the area via an attached battery implanted in the buttock. This delivers low-amplitude stimulation resulting in modulation of neural activity and stabilisation of bladder electrical activity through a mechanism that is, as yet, not fully understood. In most centres, test stimulation with a temporary or permanent electrode is performed to assess response, before undertaking permanent stimulator implantation. Currently, the only reliable predictor for treatment success in SNS is test stimulation. A SR did not find predictive factors of success due to low level of evidence of included studies (small, retrospective, and heterogeneous populations) [250].

All randomised studies suffer from the limitation that patients cannot be blinded to the treatment allocation since all recruited patients have to respond to a test phase before randomisation.

The ROSETTA trial randomised 386 women with refractory UUI to SNS (n = 194 women) or intradetrusor injection of onabotA (n = 192 women) [251]. At two years, the authors found no statistically significant difference between SNS and onabotA in improvement of mean symptom scores on OABq-SF or in reducing the mean UUI daily episodes. Patients reported significantly higher satisfaction with onabotA, but also significantly higher rates of recurrent UTIs than SNS (24% vs. 10%, respectively). On the other hand, SNS was associated with 9% removal rate and 3% revision rate at two-years follow-up.

The INSITE trial randomised 70 (94% women) patients to SNS implantation and 77 patients (92% women) to receive antimuscarinics [252]. At six months follow-up, results showed statistically significant higher success rate for SNS compared to antimuscarinics – success was defined as > 50% improvement in daily UUI or frequency episodes. Adverse events occurred in 30% and 27% of SNS and antimuscarinics trial arms, respectively, none were serious. SNS was associated with higher rates of UTIs and was associated with implant site infection and lead migration in 3.4% of cases each.

A Cochrane review [253] identified three RCTs that investigated SNS in patients with refractory UUI. The majority of studies compared a strategy of immediate implantation with delayed implantation. One study compared implantation to controls who stayed on medical treatment and received delayed implantation at six months. Fifty percent of the immediately implanted group had > 90% improvement in UUI at six months compared with 1.6% of the control group [254]. The effect on QoL measured by the SF-36, was unclear as it differed between the groups in only one of the eight dimensions. The other RCT achieved similar results, although these patients had already been included in the first report [255].

Another SR of studies including SNS with ≥ 6 months follow-up reported dry rates of 43–56% [256]. Adverse events occurred in 50% of implanted cases, with surgical revision necessary in 33–41% [257, 258]. In a sub-analysis of the RCT similar success rates were found in patients with or without urodynamic DO [259].

4.1.4.3.2.1 Summary of evidence and recommendation for sacral nerve stimulation

Summary of evidence	LE
Sacral nerve stimulation is more effective than continuation of failed conservative treatment for OAB/UUI, but no sham controls have been used.	1b
Sacral nerve stimulation is as effective as onabotA 200 U injection at 24 months.	1b
In patients who have been implanted, 50% improvement of UUI is maintained in ≥ 50% of patients and 15% may remain cured at four years.	3

Recommendation	Strength rating
Offer sacral nerve stimulation to patients who have overactive bladder/urge urinary incontinence refractory to anticholinergic therapy.	Strong

4.1.4.3.3 Laser treatment

A recent SR evaluated the use of vaginal lasers in the treatment of OAB in short term studies detailing minimal improvement [260]. No RCTs were included, the quality of reported studies were weak and long-term safety data were also lacking.

4.1.4.3.3.1 Summary of evidence and recommendation for laser treatment

Summary of evidence	LE
Vaginal laser therapy shows minimal OAB symptom improvement in the short term, with minimal complications, however, long-term efficacy and safety data is lacking.	3

Recommendation	Strength rating
Do not offer vaginal laser therapy to treat overactive bladder symptoms outside of a well-regulated clinical research trial.	Strong

4.1.4.3.4 Cystoplasty/urinary diversion

4.1.4.3.4.1 Augmentation cystoplasty

In augmentation cystoplasty (also known as clam cystoplasty), a detubularised segment of bowel is inserted into the bivalved bladder wall. Most of the evidence pertaining to cystoplasty comes from patients with neuropathic bladder dysfunction. One study did not find any difference between bivalving the bladder in the sagittal or coronal plane [261, 262]. The procedure can be done, with equal success by open or robotic techniques, although the latter takes more time [263].

There are no RCTs comparing bladder augmentation to other treatments for patients with OAB/UUI.

A large case series of bladder augmentation in a mixed population of idiopathic and neurogenic UUI included 51 women [264]. 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. The results for idiopathic DO (58%) were less satisfactory than for neurogenic UUI (90%). Malignant transformation was not reported in this series; however, it has been documented in other series and a SR [265-267]. Fewer than 60 cases have been reported worldwide, and almost all are exclusively beyond ten years after the original cystoplasty [268].

Adverse effects are common and have been summarised in a review with five to seventeen years follow-up of > 267 cases; 61 of which had non-neurogenic UUI [269]. Short-term complications include bowel obstruction (2%), infection (1.5%), thromboembolism (1%), bleeding (0.75%) and fistula (0.4%). In the long term, patients may require CISC to obtain adequate bladder emptying (38%). Other long-term effects include asymptomatic bacteriuria (70%), changes in bowel symptoms (25%), UTI (20%), metabolic disturbances (16%), urinary tract stones (13%), deterioration in renal function (2%), and bladder perforation (0.75%).

It is unclear if mucolytic agents reduce mucus accumulation. The only RCT comparing various mucolytic agents did not find significant benefits with the use of N-acetylcysteine, aspirin, or ranitidine. In one small study (n = 40), subcutaneous octreotide immediately before, and for fifteen days after surgery yielded significant reductions in mucus production, the need for bladder irrigation to clear blockages, and mean duration of hospital stay [270]. Before cystoplasty, all potential complications should be outlined, and before and after surgery, patients should be well supported by stoma/continence nurses.

Depending on the relative costs of onabotA and augmentation cystoplasty, the latter can be cost-effective within 5 years if the complication rate is low and duration of effect of onabotA is < 5 months [271].

4.1.4.3.4.2 Detrusor myectomy (bladder auto-augmentation)

Detrusor myectomy aims to increase bladder capacity and reduce storage pressure 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 [272].

Two case series in adult patients with idiopathic and neurogenic bladder dysfunction demonstrated poor long-term results caused by fibrosis of the pseudo-diverticulum [273, 274]. This technique is rarely, if ever, used nowadays.

4.1.4.3.4.3 Urinary Diversion

Urinary diversion remains a reconstructive option for patients with intractable UI after multiple pelvic procedures, radiotherapy or pelvic pathology leading to irreversible sphincteric incompetence or fistula formation. Options include ileal conduit urinary diversion, orthotopic neobladder and heterotopic neobladder with Mitrofanoff continent catheterisable conduit. There is insufficient evidence to comment on which procedure leads to the most improved QoL.

A small study comparing ileal with colonic conduits concluded that there are no differences in the relative risks (RR) of UUT infection and uretero-intestinal stenosis. However, no studies have specifically examined these techniques for treatment of intractable OAB/UUI [261]. Therefore, careful consideration of which operation is undertaken depends on thorough preoperative counselling, access to stoma/continence nurses, as well as patient factors to allow for fully informed patient choice.

4.1.4.3.4.4 Summary of evidence and recommendations for cystoplasty/urinary diversion

Summary of evidence	LE
There is limited evidence of the effectiveness of augmentation cystoplasty and urinary diversion specifically for treatment of idiopathic OAB or UUI.	3
Augmentation cystoplasty and urinary diversion are associated with high risks of short- and long-term severe complications.	3
The need to perform CISC following augmentation cystoplasty is common.	3
There is no evidence comparing the efficacy or adverse effects of augmentation cystoplasty to urinary diversion.	3

Recommendations	Strength rating
Ensure patient counselling and life-long support both prior to and after major surgery as a treatment for overactive bladder (OAB) is provided by a specialist nurse or equivalent health care provider.	Strong
Offer augmentation cystoplasty to patients with OAB/urge urinary incontinence (UUI) who have failed all other treatment options and have been informed about all possible complications.	Weak
Inform patients undergoing augmentation cystoplasty of the high risk of clean intermittent self-catheterisation (ensure they are willing and able to do so) and that they will need life-long surveillance.	Strong
Do not offer detrusor myectomy as a treatment for UUI.	Weak
Only offer urinary diversion to patients who have failed less-invasive therapies for the treatment of OAB/UUI, who will accept a stoma and have been warned about the possible small risk of malignancy.	Weak

*4.1.5 **Follow-up***

Follow-up for women with OAB is guided by the type of treatment instituted and local service capacity. Standardisation of follow-up pathways can therefore be difficult. Here, we provide recommendations based on best practice and standards from clinical trials.

4.1.5.1 Recommendations for follow-up of patients with overactive bladder

Recommendations	Strength rating
Offer early follow-up to women who have been commenced on anticholinergic or beta-3 agonist therapy.	Strong
Offer repeat injections of onabotulinumtoxinA, as required, to women in whom it has been effective (refer to the manufacturer's guidance regarding the minimum timeframe for repeat injections).	Strong
Offer life-long surveillance to women who have a sacral nerve stimulation implant to monitor for lead displacement, malfunction, and battery wear.	Strong
Offer cystoscopic surveillance to women with an augmentation cystoplasty due to the small risk of malignancy.	Weak

4.2 Stress urinary incontinence

*4.2.1 **Epidemiology, aetiology, pathophysiology***

Stress urinary incontinence, defined as the involuntary loss of urine on effort or physical exertion, is a significant health problem worldwide with social and economic impact on women and society. It is estimated that the number of women in the USA with UI will have increased from 18.3 million in 2010 to 28.4 million in 2050 [275]. The prevalence of SUI appears to peak between 45 and 59 years of age [276].

Data regarding the association of UI with ethnicity are conflicting. In several studies, SUI is more common in white women than in women of African American or Asian American origin [277, 278]. Other factors positively associated with SUI include parity, obesity, previous hysterectomy or pelvic surgery, diabetes mellitus [279] and

pulmonary disease [280]. Physical activity level is another important factor that is positively correlated with SUI severity [281]. A meta-analysis including six studies with a total sample size of 3,678 cases showed that the risk for SUI in women with metabolic syndrome was three times those without [282].

Two common, often overlapping, mechanisms for SUI have been described: (1) urethral hypermobility resulting from loss of support of the bladder neck and urethra; and (2) weakness of the urinary sphincter itself (intrinsic sphincter deficiency), which can result from trauma, radiotherapy, previous pelvic or uro-gynaecological surgery, neurological disease, or ageing.

The mechanism behind urethral hypermobility as a cause of SUI is based on the "vaginal hammock" hypothesis [283]. The endopelvic fascia, which is attached to the upper (abdominal) side of the PFMs, links the muscles to the vagina and represents the "hammock", which can compress the urethra during rest and activity. This compression, combined with intrinsic urethral sphincter pressure, supports, and maintains the urethra in the correct and closed position, preventing involuntary loss of urine, despite any increases in intravesical pressure. Damage to the supporting tissues (particularly the arcus tendinous fasciae pelvis, the central part of the fascia) can result in urethral hypermobility. Consequently, rather than being compressed at times of increased intra-abdominal pressure, the urethra moves caudally, funnelling the bladder neck, and is no longer compressed, resulting in SUI [283, 284]. In general, almost all treatments are used for both subtypes of SUI, but in general most treatments are more successful in patients with some degree of urethral hypermobility than for isolated intrinsic weakness of the urinary sphincter [285].

*4.2.2 **Classification***

Patients with SUI can be classified as uncomplicated and complicated [286]. The Panel has reached a consensus on the definition to be used throughout this guideline document:

- Women with uncomplicated SUI: no prior surgery for SUI, extensive pelvic surgery, or pelvic radiotherapy; no neurogenic LUT dysfunction; no bothersome genitourinary prolapse; absence of voiding symptoms; and no medical conditions that affect the LUT. In cases where additional significant storage symptoms, especially OAB, are present, consider a possible diagnosis of MUI (see Section 4.3).
- Women with complicated SUI: previous surgery for incontinence or extensive pelvic surgery; history of pelvic irradiation; presence of anterior or apical POP; presence of voiding symptoms or neurogenic LUT dysfunction; significant OAB/UUI; congenital abnormalities such as bladder exstrophy. Neurogenic LUT dysfunction is reviewed in the EAU Guidelines on Neuro-Urology and will not be considered further in these guidelines [9]. The treatment of LUTS associated with genitourinary prolapse has been included in these guidelines (see Section 4.7).

*4.2.3 **Diagnostic evaluation***

4.2.3.1 History and physical examination

There is universal agreement that taking a history, should be the first step in the assessment of anyone with UI. When the history categorises UI as probable SUI the presence of complicated or uncomplicated SUI can also be determined. Those patients who require rapid referral to an appropriate specialist can also often be identified from the clinical history.

There is little evidence from clinical trials that carrying out a clinical examination improves clinical outcomes, but there is widespread consensus that it remains an essential part of the assessment of women with SUI. It should include abdominal examination, vaginal examination and careful assessment of any associated POP, examination of the perineum and evaluation of PFM strength, as well as a neuro-urological examination. An attempt to reproduce the SUI should be made. A standing cough test has greater sensitivity for diagnosis of SUI compared with a supine cough test [287]. Despite this, the ICS has proposed a standardisation of the female cough stress test that includes a supine/lithotomy position with 200–400 mL fluid in the bladder and one to four coughs [288].

4.2.3.1.1 Summary of evidence and recommendation for history and physical examination

Summary of evidence	**LE**
A standing cough stress test is more sensitive than a supine test.	1b

Recommendation	Strength rating
Take a full clinical history and perform a thorough physical examination including standardised cough stress test in all women presenting with stress urinary incontinence.	Strong

4.2.3.2 Patient questionnaires

Although many studies have investigated the validity and reliability of urinary symptom questionnaires and PROMs, most of these studies did not include homogeneous populations of adult women diagnosed with SUI. This limits the extent to which results and conclusions from these studies can be specifically applied to women with SUI. Some questionnaires are used for prevalence studies; others are responsive to change and may be used to measure outcomes, although evidence on their sensitivity is inconsistent [26, 27]. There is no evidence to indicate whether use of QoL or condition-specific questionnaires has an impact on treatment outcome. To date, there is not one questionnaire that fulfils all requirements for the assessment of women with SUI.

4.2.3.2.1 Summary of evidence and recommendation for patient questionnaires

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 and associated bother of SUI.	3
Both condition-specific and general health status questionnaires measure current health status and are responsive to change following treatment.	3

Recommendation	Strength rating
Use a validated and appropriate questionnaire as part of the standardised assessment of patients with stress urinary incontinence.	Strong

4.2.3.3 Post-void residual volume

It is important to evaluate PVR volume in patients with SUI; particularly in those who also have voiding symptoms or POP. The prevalence of a significant PVR volume in patients with SUI is uncertain, partly because of the lack of a standard definition of an abnormal PVR volume. Most studies investigating PVR volume have not included patients with SUI. In general, the data on PVR volume can only be applied with caution to adults with non-neurogenic SUI. In a cohort study of > 900 women with SUI, there was good correlation between PVR volume estimated by US and measured by catheterisation [59].

4.2.3.3.1 Summary of evidence and recommendations for post-void residual volume

Summary of evidence	LE
The majority of women with SUI do not have a significant PVR volume.	3
There is good correlation between PVR volume estimated using US and measured via catheterisation in women with SUI.	3

Recommendations	Strength rating
Measure post-void residual (PVR) volume, particularly when assessing patients with voiding symptoms or complicated stress urinary incontinence (SUI).	Strong
When measuring PVR volume, use ultrasound in preference to catheterisation.	Strong
Monitor PVR volume in patients scheduled for treatment that may cause or worsen voiding dysfunction, including surgery for SUI.	Strong

4.2.3.4 Urodynamics

The role of urodynamics in SUI evaluation remains poorly defined and is still under debate.

Invasive urodynamic tests are often performed prior to surgical treatment of SUI. Clinical diagnosis of incontinence and cystometric findings often do not correlate [66, 67]. The diagnostic accuracy of urethral pressure profilometry [68] and VLPP measurement in SUI is generally poor [289]. Measurement of MUCP correlates, albeit weakly, with incontinence severity [68], and there is conflicting evidence about its

reproducibility [64, 65]. Methods of recording MUCP cannot be compared meaningfully [290]. Valsalva leak point pressures are not standardised and there is minimal evidence about reproducibility. Valsalva leak point pressures did not reliably assess incontinence severity in a cohort of women selected for surgical treatment of SUI [69]. The predictive value of the tests regarding treatment outcome remains unclear.

A Cochrane review including seven RCTs showed that urodynamic tests increased the likelihood of avoiding surgery for SUI. However, there is no evidence that this influence on decision-making alters the clinical outcome of treatment within trial populations [77].

A high-quality RCT (n = 630) compared office evaluation alone and combined with urodynamics in women with clinically demonstrable SUI about to undergo surgery. While urodynamics changed the clinical diagnosis in 56% of women [291], there was no difference in severity of SUI or any secondary outcome at twelve months' follow-up after SUI surgery [79]. A similar study also found that omission of urodynamics in the preoperative work-up of SUI did not lead to inferior results [292]. Patients in whom urodynamics were discordant with clinical assessment (n = 109) were randomly allocated to receive either immediate surgery or individually tailored therapy based on the urodynamic findings. In this trial, performing immediate surgery, irrespective of the result of urodynamics, did not result in inferior outcomes [293]. An RCT, in which 145 women were randomised to retropubic or trans-obturator MUS, concluded that when patients were stratified according to preoperative VLPP (≤ or > 60 cm H_2O), it was not linked to outcome after both synthetic MUS procedures [294].

Another study reported conflicting evidence. Valsalva leak point pressures or MUCP in the lowest quartile was predictive in terms of synthetic MUS failure at twelve months [83].

The Panel recognises that it may be valuable to use urodynamic test results to help select the optimum surgical procedure, but the evidence outlined above suggests that performing urodynamics in patients with uncomplicated SUI, which can be diagnosed based on detailed clinical history and demonstrated at examination, is not necessary. The role of urodynamics in complicated SUI is still under debate [295]. However, the Panel consensus is that urodynamics should be carefully considered in cases of SUI with associated storage symptoms; cases in which the type of incontinence is unclear; cases in which voiding dysfunction is suspected; and cases with associated POP or prior surgery for SUI. This is in line with other guideline documents in this area [66].

4.2.3.4.1 Summary of evidence and recommendations for urodynamics

Summary of evidence	**LE**
Preoperative urodynamic testing in women with uncomplicated, clinically demonstrable, SUI does not improve surgical outcome for SUI.	1b
There is no consistent correlation between urethral function tests and subsequent success or failure of SUI surgery.	3
There is no consistent evidence that preoperative DO is associated with surgical failure of MUS in women.	3

Recommendations	**Strength rating**
Perform preoperative urodynamic tests in cases of SUI with associated storage symptoms, cases in which the type of incontinence is unclear, cases in which voiding dysfunction is suspected, and cases with associated pelvic organ prolapse or prior surgery for SUI.	Weak
Perform urodynamic tests if the findings may change the choice of invasive treatment.	Weak
Do not use urethral pressure profilometry or leak point pressure to grade severity of incontinence as they are primarily tests of urethral function.	Strong

4.2.3.5 Pad testing

Please refer to Section 3.7 for the diagnostic accuracy and predictive value of using pad testing to quantify the presence and severity of SUI. The summary of evidence and recommendations can be found in section 3.7.1.

4.2.3.6 Imaging

The role of imaging in SUI patients is limited. Many studies have evaluated imaging of bladder neck mobility by US and MRI and concluded that SUI cannot be identified by a particular pattern of urethro-vesical movement [296]. In addition, the generalised increase in urethral mobility after childbirth does not appear to be associated with de novo SUI [297]. Studies have assessed the use of imaging to investigate the mechanism of action of MUS inserted for SUI. One study suggested that MUS placement decreased mobility of the mid-urethra but not mobility of the bladder neck [109]. Following MUS surgery, a wider gap between symphysis and sling (assessed by imaging) has been shown to correlate with a lower chance of cure of SUI [110]. One study of 72 women post-synthetic sub-urethral MUS surgery has investigated the usefulness of trans-labial US to assess tape functionality. In this study different parameters were measured (distance from tape to urethra, position, and shape during Valsalva manoeuvre, etc.) and concluded that tape position relative to the patient's urethra seems to play a role in treatment outcome [298]. The general role of US in the evaluation and follow-up of women with SUI is unclear, and further research is needed to establish its place in the clinical pathway.

Several imaging studies have investigated the relationship between sphincter volume and function [299] and sphincter volume and outcome of surgery [300] in women. However, no imaging test has been shown to predict the outcome of treatment for SUI. 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 SUI.

4.2.3.6.1 Summary of evidence and recommendation for imaging

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

Recommendation	**Strength rating**
Do not carry out imaging of the upper or lower urinary tract as part of the routine assessment of stress urinary incontinence.	Strong

*4.2.4 **Disease management***

4.2.4.1 Conservative management

4.2.4.1.1 Obesity and weight loss

Being overweight or obese has been identified as one of the risk factors for LUTS and SUI in many epidemiological studies [136, 137]. There is evidence that the prevalence of both UUI and SUI increases proportionately with BMI [301]. The proportion of patients who undergo surgery for incontinence who are overweight or obese is higher than that of the general population [137]. On the other hand, young, elite athletes, and women who work-out for fitness show a high prevalence of UI/SUI [281, 302].

Three SRs concluded that weight loss was beneficial in improving UI [135, 136, 303]. Five further RCTs reported a similar beneficial effect on incontinence following surgical weight reduction programmes [304-308].

In a prospective study in 160 consecutive women who underwent bariatric surgery, surgically induced weight loss was associated with a significant improvement in pelvic floor disorders, including UI [309]. Similar results reported by prospective single-centre studies investigating the effect of weight loss induced by bariatric surgery revealed that bariatric surgery was associated with substantially reduced UI at eleven months and three years [310, 311].

4.2.4.1.1.1 Summary of evidence and recommendation for obesity and weight loss

Summary of evidence	**LE**
Obesity is one of the risk factors for LUTS and UI in women.	3
Non-surgical weight loss improves UI in overweight and obese women.	1a
Surgical weight loss improves UI in obese women.	1b

Recommendation	Strength rating
Encourage overweight and obese women with LUTS/stress urinary incontinence to lose weight and maintain weight loss.	Strong

4.2.4.1.2 Urinary containment

The evidence for urinary containment derives from the same literature as for containment in OAB-wet. The readers are therefore referred to Section 4.1.4.1.3. The summary of evidence and recommendations for urinary containment can be found in Section 4.1.4.1.3.1.

4.2.4.1.3 Pelvic floor muscle training

Pelvic floor muscle training is used to improve functional and morphological parameters of the pelvic floor, thus improving urethral stability.

An immediate effect of a single PFM contraction is narrowing of the levator hiatus area, increase of urethral closure pressure, and lifting of the bladder and rectum thus preventing occurrence of SUI [312-314]. In an RCT comparing intensive PFMT over a six-month period with no treatment, there were increased muscle strength and endurance, narrowing of the levator hiatus, reduced PFM length, increased muscle volume, and lifting of the bladder neck and rectal ampulla [315]. Pelvic floor muscle training may be used to prevent SUI, e.g., in childbearing women before birth, or as part of a planned recovery programme after childbirth. Most often, PFMT is used to treat existing SUI; sometimes in combination with observation and/or palpation of the muscle contraction by the therapist, or biofeedback (using an apparatus measuring the contraction either by electromyography, manometry, dynamometry, US or MRI). Electrical stimulation and vaginal cones are also used in treatment of SUI based on an assumption of the same mechanism of action.

4.2.4.1.3.1 Efficacy of pelvic floor muscle training

A Cochrane review compared PFMT with no treatment or inactive control treatment and found that women with SUI in the PFMT groups were eight times more likely to report cure [316]. The review also documented significant improvement in SUI and improvement in UI QoL. Pelvic floor muscle training reduced leakage by an average of one episode per day in women with SUI. Women with SUI in the PFMT groups lost significantly less urine in short (up to one-hour) pad tests. The comparison of short pad tests showed considerable heterogeneity, but the findings still favoured PFMT when using a random-effects model. Women in the PFMT group were also more satisfied with treatment and their sexual outcomes were better. Adverse events were rare and minor.

A Cochrane review concluded that there may be some additional effect of adding biofeedback to PFMT. However, this was based on RCTs with training frequency and attention favouring biofeedback [317]. In a recent RCT (61.3% had MUI) comparing the exact same training dosage and attention between groups, use of biofeedback did not yield any additional effect [318]. Group training is cost-effective in treatment of SUI/UI compared to individual treatment [319]. Another Cochrane review concluded that combination of individual assessment/education and group training was equally effective compared to individual treatment, but again the dosage and attention differed between comparison groups [320]. In a more recent RCT with the exact same training dosage and attention in individual and group training, group training was not inferior to individual treatment [319]. It is worth noting that all of the PFMT interventions in these reviews follow individual assessment and teaching before starting PFMT, and most interventions use some sort of measurement tool (biofeedback) in the assessment.

Both the Cochrane review and the ICI concluded that the use of vaginal cones to train the PFMs is more effective than no treatment, but it is inconclusive whether it is more or less effective than structured PFMT [316, 321, 322]. Some women are unable to maintain the cone inside, and some report discomfort and motivation problems and adherence may be low [321].

The Cochrane review [316], the ICI [322] and the National Institute for Health and Care Excellence (NICE) guidelines (2019) [66] all conclude that there is the highest level evidence (1a) to support PFMT in the treatment of SUI/MUI. All SRs conclude that PFMT is less effective if women with MUI and UUI are included in the studies and more effective with more intensive and supervised training. According to the NICE guidelines literature review, PFMT is as effective as surgery for around half of women with SUI, and due to the risks following surgery and absence of adverse effects of PFMT, they recommend three months of supervised PFMT as first-line treatment for SUI and MUI [66].

Pelvic floor muscle training was compared to synthetic MUS surgery in an RCT involving 460 women with moderate to severe SUI [323]. Crossover between treatment arms was allowed and 49% of women in the physiotherapy group and 11.2% of women in the surgery group crossed over to the alternative treatment.

Subjective improvement was reported by 90.8% of women in the surgery group and 64.4% of women in the physiotherapy group at twelve months [323].

4.2.4.1.3.2 Efficacy of electrical stimulation

There is lack of consensus regarding the use of ES to treat SUI. For subjective cure of SUI, a Cochrane review found moderate-quality evidence that ES is probably better than no active treatment [324]. Similar results were found for cure or improvement of SUI, but the quality of evidence was low. There is uncertainty as to whether there is a difference between ES and sham treatment in terms of subjective cure alone because of the very low quality of evidence. For subjective cure or improvement, ES may be better than sham treatment. Any comparison between ES and PFMT and other treatments is hampered by low-quality evidence. One assessor blinded RCT found that PFMT was significantly better than either the use of vaginal cones or electrical stimulation. Only PFMT showed improvement in PFM strength and SUI measured by pad test and leakage episodes compared to control [325]. Adverse effects such as pain and discomfort have been reported, and ES is not tolerated by all women [324].

In an RCT, 132 women assessed by vaginal palpation to have 0–1 on the modified Oxford grading scale (unable to contract the PFM) were randomly assigned to an eight-week intervention of learning to contract via palpation, palpation with pelvic tilt, intravaginal ES, or verbal instruction [326]. The results showed that 63.6%, 69.7%, 33.3% and 18.2% in the four groups, respectively, scored 2 after the intervention. Palpation was significantly more effective that ES, but one third of the ES group had learned a correct PFM contraction [326]. The effect on UI measured by ICIQ-UI-SF was significantly better in the palpation group. An RCT [327] compared electrical stimulation with untreated control in 64 women with 0-1 on the modified Oxford grading scale. After the intervention, the ability to contract the PFMs was acquired by 36% of the experimental group and 12% of the control group. The experimental group also improved by a mean of 2 points more than the control group on the ICIQ-UI-SF score.

4.2.4.1.3.3 Long-term efficacy of pelvic floor muscle training

In a SR including nineteen studies, 1,141 women were followed-up for one to fifteen years after PFMT for SUI [328]. Meta-analysis was not performed due to high heterogeneity of outcome measures and training dosage (frequency, intensity, duration, and adherence). Only two studies provided interventions during follow-up. Losses to follow-up ranged between 0% and 39%. Long-term adherence to PFMT varied between 10% and 70%. Five studies reported that the initial success rate on SUI and MUI was maintained in the long term. Long-term success based on responders in the original trial varied between 41% and 85%. Surgery rates in the long term varied between 4.9% and 58%. It was concluded that short-term outcome of PFMT can be maintained at long-term follow-up without incentives for continued training, but there is a high heterogeneity in both interventional and methodological quality in short- and long-term PFMT studies [328].

4.2.4.1.3.4 Efficacy of pelvic floor muscle training in childbearing women

Pelvic floor muscle training to prevent SUI has been studied during pregnancy and in the postpartum period and the results are not reported separately for SUI and other subgroups of UI. A Cochrane review concluded that PFMT in women with and without UI (combined primary and secondary prevention) during pregnancy, produced a 26% reduced risk of UI during pregnancy and the mid-postnatal period [329]. Furthermore, pregnant continent women (primary prevention) who exercised the PFM during pregnancy were 62% less likely to experience UI in late pregnancy and had 29% lower risk of UI three to six months after giving birth. There is insufficient evidence for a long-term effect of antenatal PFMT beyond six to twelve months postpartum. Compared with usual care, there is no evidence that antenatal PFMT in incontinent women decreases incontinence in late pregnancy (very low-quality evidence), or in the mid- (low-quality evidence) or late postnatal periods (very low-quality evidence).

There have been fewer RCTs in the postpartum period than during pregnancy [329]. No primary prevention studies were found in women after birth. For PFMT started after delivery, in a mixed group of continent and incontinent women, there was uncertainty about the effect on UI risk in the late postnatal period (three trials, 826 women; moderate-quality evidence), and in postnatal women with persistent UI, there is no evidence that PFMT results in a difference in UI at more than six to twelve months postpartum (three trials; 696 women; low-quality evidence). However, another RCT found that UI was less frequent in the intervention group, with 57% of patients still symptomatic, compared to 82% of controls, as was bladder-related problems with a prevalence of 27% in the intervention vs. 60% in the control group [330]. Randomised controlled trials of high interventional and methodological quality are needed in the postpartum period.

4.2.4.1.3.5 Efficacy of Pelvic floor muscle training in elderly women

There have been few RCTs on conservative treatment of SUI in elderly women (> 65 years) and many of the studies combined different modalities, such as BT, lifestyle modifications and PFMT [331]. Some of the studies on PFMT and SUI in the general population have included women > 65 years and PFMT seems to be equally effective in elderly women. A SR on conservative management included 23 trials, with nine of moderate-to-high methodological quality and concluded that PFMT in combination with physical training was effective in reducing UI and improving QoL [332]. Prompted voiding and toileting assistance with functional exercise reduced UI. Other behavioural interventions such as night-time prompted voiding and waking routine had no effect on UI reduction. The most recent ICI consensus publication stated that although there are limited studies of PFMT on UI in frail elderly populations, age and frailty alone should not preclude the use of PFMT in appropriate patients with sufficient cognition to participate [331]. More high-quality RCTs, both in frail and healthy older women (> 80 years of age) are needed.

4.2.4.1.3.6 Composite treatments for PFMT

A Cochrane review found insufficient evidence to state whether there were additional effects by adding PFMT to other active treatments (including vaginal cones, electromagnetic stimulation, biofeedback, continence pessary, drugs) when compared with the same active treatment alone for female SUI or mixed UI. However, these results should be interpreted with caution as most of the comparisons were investigated in small, single trials. Also, none of the included trials reported data on adverse events associated with the PFMT regimen, thereby making it very difficult to evaluate the safety of PFMT [333].

A single-blind RCT evaluated whether peri-operative supervised PFMT was superior to standard care (handout) in terms of improvements in SUI symptoms, cure rate, and/or post-operative filling or voiding symptoms among women undergoing synthetic MUS insertion for SUI. The results showed that supervised PFMT improves SUI cure rates associated with synthetic MUS insertion with OR > 3 when considering symptoms of SUI, but does not improve post-operative continence function as measured by a pad test, nor does it lead to fewer post-operative voiding or filling symptoms [334].

4.2.4.1.3.7 Summary of evidence and recommendations for pelvic floor muscle training

Summary of evidence	**LE**
Pelvic floor muscle training is better than no treatment for improving SUI and QoL in women with SUI and MUI across a range of outcomes, including cure rate, improvement rate, QoL, number and volume of urine leaks and treatment satisfaction.	1a
Pelvic floor muscle training exhibits a low rate of adverse events.	1a
Higher-intensity, supervised treatment regimens confer greater benefit in women receiving PFMT.	1a
There is no extra benefit of combining PFMT with biofeedback.	1b
Short-term benefits of intensive PFMT can be maintained in the long term.	2a
Pelvic floor muscle training in the antenatal period is associated with a reduced risk of UI in late pregnancy and in the short term postnatally.	1a
Postpartum PFMT is effective in women with persistent UI.	1b
The benefit of postpartum PFMT in mixed populations (continent and incontinent) of women is uncertain.	1b
Mid-urethral sling surgery is superior to PFMT in women with moderate-to-severe SUI.	1b
Pelvic floor muscle training commencing in the early postpartum period improves UI in women for up to six months.	1b
There is conflicting evidence on whether the addition of ES increases the effectiveness of PFMT alone.	2a
There is low to moderate certainty evidence suggesting benefit of ES in patients with SUI. In addition, ES may be useful for learning a correct PFM contraction.	1b

Recommendations	Strength rating
Offer supervised intensive pelvic floor muscle training (PFMT), lasting at least three months, as first-line therapy to all women with stress urinary incontinence (SUI) or mixed urinary incontinence (including elderly women and pre- and postnatal women).	Strong
Ensure that PFMT programmes are as intensive as possible.	Strong
Balance the efficacy and lack of adverse events from PFMT against the expected effect and complications from invasive surgery for SUI.	Strong
Consider electrical stimulation for treatment of SUI, or as an adjunct for teaching PFM contraction.	Weak

4.2.4.1.4 Electromagnetic stimulation

Electromagnetic stimulation (EMS) has been evaluated for its role in SUI therapy. In a double-blind RCT of EMS including 70 women with SUI, no effect of EMS over sham in any outcome was recorded [335].

4.2.4.1.5 Electroacupuncture

A SR including 15 RCTs and women with SUI treated by electroacupuncture (EA) demonstrated that EA for SUI was effective. The ICIQ-SF scores improved, and 1-hour urine leakage decreased in patients undergoing EA compared with those receiving sham EA, physical exercise or medication [336].

4.2.4.2 Pharmacological management

4.2.4.2.1 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 SUI have 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 [236-238]. Vaginal (local) treatment is primarily used to treat symptoms of vaginal atrophy in postmenopausal women.

A Cochrane SR looked at the use of oestrogen therapy in postmenopausal women given local oestrogen therapy and seventeen studies focused on SUI [236]. There is also a narrative review of oestrogen therapy in urogenital diseases [337]. The Cochrane review found that vaginal oestrogen treatment improved symptoms of SUI in the short term [236]. There were small, low-quality trials comparing vaginal oestrogen treatment with phenylpropanolamine, PFMT, ES 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. In one trial, no significant adverse effects following vaginal administration of oestradiol for vulvovaginal atrophy over a two year period were reported [338].

Vaginal oestrogen therapy can be given as conjugated equine oestrogen, oestriol or oestradiol in vaginal pessaries, vaginal rings, or creams. The ideal treatment duration and the long-term effects are uncertain. A review of local oestrogen treatment showed improvement of UI over placebo with vaginal rings, which were favoured subjectively over pessaries [339].

One RCT in postmenopausal women showed a benefit of adding intravaginal oestriol to vaginal ES and PFMT in female SUI [340].

Studies of systemic 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 and no SUI improvement [341-346]. In a single RCT, use of raloxifene was not associated with development or worsening of UI [347]. Two small RCTs using oral oestriol or oestradiol as HRT for vulvovaginal atrophy suggested that UI symptoms were improved although the evidence was unclear [66, 348].

4.2.4.2.1.1 Summary of evidence and recommendations for oestrogens

Summary of evidence	LE
Vaginal oestrogen therapy improves SUI for postmenopausal women in the short term.	1a
Neoadjuvant or adjuvant use of local oestrogens is ineffective as an adjunct to surgery for SUI.	2b
Systemic HRT using conjugated equine oestrogens does not improve SUI and may worsen pre-existing UI.	1a

Recommendations	Strength rating
Offer vaginal oestrogen therapy to postmenopausal women with stress urinary incontinence (SUI) and symptoms of vulvovaginal atrophy.	Strong
In women taking oral conjugated equine oestrogen as hormone replacement therapy (HRT) who develop or experience worsening SUI, discuss alternative HRT.	Strong

4.2.4.2.2 Duloxetine

Duloxetine inhibits the presynaptic reuptake of neurotransmitters, serotonin (5-hydroxytryptamine; 5-HT) and noradrenaline (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 neurons, which in turn increases the resting tone and contraction strength of the urethral striated sphincter.

Duloxetine was evaluated as a treatment for female SUI or MUI in three SRs [171, 349, 350]. Improvement in UI compared to placebo was observed with no clear differences between SUI and MUI. One study reported cure for UI in 10% of patients. An improvement in the UI QoL questionnaire was not found in the study, which used this as a primary endpoint. In a further study comparing duloxetine, 80 mg daily, with PFMT alone, PFMT + duloxetine, and placebo [351], 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 in this trial.

Two open-label studies with a follow-up of ≥ 1 year evaluated the long-term effect of duloxetine in controlling SUI [352, 353]. Both studies had a high patient withdrawal rate, due to lack of efficacy and a high incidence of adverse events, including nausea and vomiting (≥ 40% of patients), dry mouth, constipation, dizziness, insomnia, somnolence, and fatigue.

A SR showed significant efficacy for duloxetine compared to placebo in women with SUI, but with increased risk of adverse events [350]. The adverse effects of duloxetine include mental health problems and suicidal ideation. A meta-analysis of four RCTs including 1,910 women with SUI reported no suicidality, violence, or akathisia events, but suggested that discontinuation rate due to adverse events was around one in seven and that the harm may outweigh the benefit of treatment [354]. A meta-analysis of twelve placebo-controlled trials involving almost 3,000 patients showed that in patients with major depressive disorders there were no significant differences in the incidence of suicide-related events with duloxetine vs. placebo [355].

4.2.4.2.2.1 Summary of evidence and recommendations for duloxetine

Summary of evidence	LE
Duloxetine improves SUI in women, but the chances of cure are low.	1a
Duloxetine may cause significant gastrointestinal and central nervous system adverse effects, leading to a high rate of treatment discontinuation, although these symptoms may be limited to the first weeks of treatment.	1a

Recommendations	Strength rating
Offer duloxetine (where licensed) to selected patients with stress urinary incontinence unresponsive to other conservative treatments and who want to avoid invasive treatment, counselling carefully about the risk of adverse events.	Strong

Duloxetine should be initiated and withdrawn using dose titration because of the high risk of adverse events.	Strong

4.2.4.2.3 Adrenergic agonists

A Cochrane SR including 22 RCTs involving 673 women and seven different adrenergic drugs (phenylpropanolamine in eleven trials, midodrine in two, norepinephrine in three, clenbuterol in another three, terbutaline in one, eskornade in one and Ro 115-1240 in one) found weak evidence that adrenergic agonists may improve SUI. Moreover, side effects did occur but were usually minor. More evidence is needed to compare adrenergic drugs with other drugs for SUI and, also with PFMT [356].

4.2.4.3 Surgical management

4.2.4.3.1 General considerations

The use of polypropylene mesh as synthetic MUS for the treatment of SUI has recently come under scrutiny following concerns about long-term complications. In some European countries such as the UK, the use of synthetic MUS has been paused and pelvic mesh was the subject of a parliamentary review published in July 2020 [357]. This review concluded that *"For many women mesh surgery is trouble free and leads to improvements in their condition. However, this is not the case for all. There is no reliable information on the true number of women who have suffered complications. While they may be in the minority, that does not diminish the catastrophic nature of their suffering or the importance of providing support to them and learning from what has happened to them"*.

The range of complications highlighted during the process of this parliamentary review included [357]:

- pain;
- recurrent infections;
- mobility issues;
- recurring or new incontinence/urinary frequency;
- recurring or new prolapse;
- haemorrhage;
- bowel issues;
- erosion of mesh; this can be into the vagina and/or other organs;
- sexual difficulties; including pain on intercourse and a loss of sex life;
- autoimmune issues;
- psychological impacts.

When considering the choice of surgical treatments for SUI the Panel advises individual clinicians to abide by any national or local rules that may be in place regarding mesh surgery. It is essential for clinicians to point out the deficiencies in the long-term evidence regarding mesh use in SUI with specific reference to the complications highlighted above.

In line with the recommendations from NICE [66] and the Scientific Committee on Emerging and Newly Identified Health Risks (SCENIHR) paper [358], the Panel agrees that surgeons and centres performing surgery should:

- be trained in the field of incontinence and for each surgical procedure they perform/offer;
- 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 long-term follow-up.

The establishment of accurate and complete databases registering the interventions, patient profiles and surgical complications or all surgical treatments for SUI is recommended to allow the generation of robust long-term data.

Many surgical procedures are available for uncomplicated SUI patients and the Panel analysed the results of the different procedures in terms of clinical effectiveness, safety and cost-effectiveness based on the recent ESTER SR and economic evaluation [359] and previous SRs including those from the Cochrane Collaboration [360-364].

The outcome parameters used to evaluate surgery for SUI have been limited to:

- continence rate;
- patient-reported outcome measures;
- general and procedure-specific complications;
- generic, specific (UI) and associated (sexual and bowel) QoL.

In this context, it has to be taken into account that a number of products may no longer be available and therefore the recommendations may not be transferable to current devices. The Panel makes a strong recommendation that new devices are only used as part of a structured research programme and their outcomes monitored in a registry, until there is adequate evidence of safety and efficacy.

4.2.4.3.1.1 Shared decision making

The Panel recognises that a shared decision-making approach is paramount when any treatments are proposed but felt particular emphasis should be made for the topic area of surgical treatment for SUI. There are a number of different options available for patients which vary in both efficacy and safety profile. Consequently, the amount of information given to patients considering surgery for SUI is substantial. The Panel would unequivocally advise adherence to the fundamental principles of the shared decision-making process which include:

- full participation from the patient;
- delivery of factual information regarding benefits and risks of any particular treatment, if possible adapted to the specific situation of the patient;
- delivery of information about the experience and expertise of the HCP/institution delivering the treatment, especially for highly specialised procedures such as complex SUI and mesh removal surgery;
- confirmation that the patient understands the information given;
- clinician understanding and documenting individual patient preferences;
- facilitation of deliberation and initial decision-making;
- patient opportunity to consider and confirm any decisions made;
- clinician assistance with implementation of the final decision.

4.2.4.3.1.2 Recommendations for surgical treatment

Recommendations	**Strength rating**
Offer patients who have explored/failed conservative treatment options a choice of different surgical procedures, where appropriate, and discuss the advantages and disadvantages of each approach.	Strong
Use new devices for the treatment of stress urinary incontinence (SUI) only as part of a structured research programme. Their outcomes must be monitored in a registry or as part of a well-regulated research trial.	Strong
Employ a shared decision-making approach when deciding on appropriate treatment for SUI.	Strong

4.2.4.3.2 Surgery for women with uncomplicated stress urinary incontinence

The principal procedures evaluated are:

- open and laparoscopic colposuspension;
- autologous “traditional” slings;
- bulking agents;
- synthetic MUS.

4.2.4.3.2.1 Open- and laparoscopic colposuspension surgery

Open Burch colposuspension was previously considered the most appropriate surgical intervention for SUI, and was used as the comparator in RCTs of newer, less-invasive surgical techniques. These include laparoscopic techniques, which have enabled colposuspension to be performed with a minimally-invasive approach.

Open colposuspension

A number of SRs have covered open surgery for SUI, with a large number of RCTs [359, 361-364]. The Cochrane review on open colposuspension [364] included 55 trials comprising 5,417 women. In most of these trials, open Burch colposuspension was used as the comparator to an experimental procedure. Within the first year, complete continence rates of 85–90% were achieved for open colposuspension, while failure rates in terms of recurrent UI were 17% up to five years and 21% at > 5 years. The risk of reoperation after Burch colposuspension is estimated at 6% within five years [77] and 10.8% within nine years [365]. The reoperation rate specifically for UI was only 2%. Burch colposuspension was associated with a higher rate of development of enterocoele/vault/cervical prolapse (42%) and rectocele (49%) at five years compared to TVT (23% and 32%, respectively). The rate of cystocoele was similar after Burch colposuspension (37%) and after TVT (41%). The Cochrane review concluded that open colposuspension is an effective treatment for SUI and around 70% of women can expect to be dry at five years after surgery.

Laparoscopic colposuspension

A Cochrane review reported on twelve trials comparing laparoscopic to open Burch colposuspension [362]. Although these procedures had a similar subjective cure rate, there was limited evidence suggesting the objective outcomes were poorer for laparoscopic colposuspension. The ESTER SR [359], based on a network meta-analysis, showed that at twelve months open colposuspension was more effective than laparoscopic colposuspension (nine trials) but these findings were based on low-quality evidence. The Surface Under the Cumulative Ranking (SUCRA) score, which is a numerical representation of the overall performance of the treatment, and represents a single number associated with each intervention, was 76.7% after open colposuspension and 48.9% after laparoscopic colposuspension. Laparoscopic colposuspension had a shorter duration and subsequent hospital stay and may be slightly more cost-effective when compared with open colposuspension after 24 months' follow-up.

Single-port laparoscopic Burch can be an alternative treatment, although data confirming efficacy are limited [366].

Complications

Voiding difficulties are more common after laparoscopic colposuspension than after retropubic MUS (7.5% vs. 5.1%) [359]. There was no difference between open colposuspension and retropubic MUS (7.8% vs. 7.5%; OR: 0.87) [359]. The results for the comparisons of *de novo* symptoms of urgency or UUI between open colposuspension and retropubic MUS (11% vs. 8%, OR: 1.49) did not favour either treatment and showed wide confidence intervals [359]. The rate of bladder or urethral perforation was higher for laparoscopic colposuspension compared with open colposuspension (3.7% vs. 0.7%; OR: 4.65) [359].

4.2.4.3.2.1.1 Summary of evidence and recommendation for open and laparoscopic colposuspension surgery

Summary of evidence	**LE**
High subjective cure rates are associated with both open and laparoscopic colposuspension for treatment of SUI.	1a
Objective cure rates are higher for open compared to laparoscopic colposuspension.	1a
Colposuspension is associated with a higher long-term risk of POP than MUS.	1a
Laparoscopic colposuspension has a shorter hospital stay and may be more cost-effective than open colposuspension.	1a
Laparoscopic colposuspension is associated with higher rates of intraoperative bladder perforation and postoperative voiding dysfunction compared to open colposuspension.	1a
The rates of *de novo* urinary urgency following colposuspension are similar to other surgical treatments for SUI.	1a

Recommendation	**Strength rating**
Offer colposuspension (open or laparoscopic) to women seeking surgical treatment for SUI following a thorough discussion of the risks and benefits relative to other surgical modalities.	Strong

4.2.4.3.2.2 Autologous sling

In the past, autologous, cadaveric, xenograft, and synthetic materials have been used for bladder neck pubovaginal sling. Nowadays, use of autologous tissue, either rectus sheath or fascia lata, is the most studied material with the strongest evidence base to support its use [367]. The ESTER SR included three trials of autologous sling vs. open colposuspension, six trials of autologous sling vs. retropubic MUS and one trial of autologous sling vs. transobturator MUS. The quality of evidence was overall very low. The pooled estimate showed that fascial sling had a higher cure rate at one year than open colposuspension (OR: 1.24), retropubic MUS (OR: 1.06) and transobturator MUS (OR: 1.44) but without significance. The SUCRA score was 89.4% for women cured after autologous fascial sling. A sub-analysis from a Cochrane review showed autologous slings had better effectiveness compared to colposuspension at one to five years' follow-up [364]. In an RCT of Burch colposuspension vs. autologous slings, complete continence rates decreased substantially over time in both arms. At five years, the continence rate of colposuspension was 24.1% compared to 30.8% for fascial slings. Satisfaction remained higher in the sling group (83% vs. 73%) and was directly related to continence status [368].

Complications
Adverse events rates were similar for the two treatment groups (Burch 10% and sling 9%) although postoperative obstruction was found exclusively in the sling group. Voiding difficulties appear to be more common after autologous sling (15.4% vs. 10.2%; OR: 1.46) than after retropubic MUS. Compared with open colposuspension, the rate of bladder or urethral perforation was lower for traditional sling (0.6% vs. 3.0%; OR:0.20) [359].

4.2.4.3.2.2.1 Summary of evidence and recommendation for autologous sling

Summary of evidence	**LE**
High cure rates are associated with autologous sling placement for treatment of SUI.	1a
Autologous sling is more effective in terms of cure rate than colposuspension.	1a
Autologous sling has a similar rate of adverse events compared to open colposuspension, with higher rates of voiding dysfunction and postoperative UTI, but lower rates of POP and bladder or urethral perforation.	1a

Recommendation	**Strength rating**
Offer autologous sling placement to women seeking surgical treatment for stress urinary incontinence following a thorough discussion of the risks and benefits relative to other surgical modalities.	Strong

4.2.4.3.2.3 Urethral bulking agents
The concept of this procedure originates from the idea that intra- or peri-urethral injection of an agent able to form artificial cushions under/around the urethra increases resistance at the bladder outlet and facilitates continence.

In a Cochrane SR [369], 2,004 patients were included from fourteen trials of seven different types of intraurethral injection: Ethylene vinyl alcohol copolymer (Uryx™), glutaraldehyde cross-linked collagen (Contigent©), a porcine dermal implant (Permacol©), solid silicone elastomer (Macroplastique©), autologous fat, pyrolytic carbon (Durasphere©), calcium hydroxylapatite (Coaptite©), Polytetrafluoroethylene (Polytef™) and hyaluronic with dextran polymer (Zuidex©). The conclusions state that the available evidence base remains insufficient to guide practice [369].

A recent SR of 56 studies conclude that available data support the use of Bulkamid® and Macroplastique®, which have shown a short-term efficacy of 30%–90% and 40%–85%, respectively, and long-term efficacy of 42%–70%, and 21%–80%, respectively. Bulkamid® appears to have a more favourable safety profile, with no cases of erosion or migration of product associated with its use. Direct comparisons of urethral bulking agents were not performed [370].

A SR of 23 studies using Macroplastique© including 958 patients showed a 75% improvement with 43% dry rate at < 6 months and a 64% improvement and 36% cure rate at > 18 months [371]. A review of 514 elderly women with SUI treated with various agents showed a reduced pad weight in 73% at one-year follow-up, independent of the material injected [372]. The heterogeneity of the populations, the variety of materials used and the lack of long-term follow-up limit guidance for practice. Most of the studies showed a tendency for short-term improvement in UI, with the exception of one RCT, which did not find a difference between saline and fat injection [373].

One trial of 30 women showed a weak, non-significant advantage in terms of patient satisfaction after mid-urethral injection in comparison to bladder neck injection but with no demonstrable difference in continence levels [369]. One small trial found 30% (six out of 20) of patients developed retention of urine following peri-urethral injection compared with 5% (one out of 20) with transurethral injection [374]. A small RCT found no difference in efficacy between mid-urethral and bladder neck injection of collagen [375]. One study treated patients who had received radiotherapy with injection of Bulkamid® and reported ~25% cure at short-term follow-up [376].

Bulking agent injection is generally safe, and the most frequent adverse event is UTI. However, autologous fat or hyaluronic acid should not be used due to the risk of fatal embolism and local abscess formation, respectively [373, 377].

A study reported that women treated by a high-volume surgeon (defined > 75 urethral bulking injections performed over surgical career) had an increased chance of cure and a lower risk of hospital contact postoperatively, compared with women treated by a low-volume surgeon. The risk of 30-day hospital contact was also lower for women treated in a high-volume department (defined > 15 procedures performed per year) [378].

Comparison with other surgical procedures
Two RCTs compared collagen injection to conventional surgery for SUI (silicon particles vs. autologous sling and collagen vs. other surgical procedures). The studies reported greater efficacy but higher complication rates for open surgery [379, 380].

In a recent non-inferiority clinical trial, women with primary SUI were randomised to TVT or polyacrylamide hydrogel urethral bulking agent injection (Bulkamid®) [381]. Mid-urethral TVT slings were associated with better satisfaction and cure rates than Bulkamid® in primary SUI. For objective cure rate, the cough stress test was negative in 95.0% of patients who underwent TVT vs. 66.4% who underwent Bulkamid®.

Another SR examining the relative efficacy of urethral bulking agents [382] included six studies in the quantitative synthesis for a total of 710 patients. The authors found that bulking agents are less effective than other surgical procedures according to subjective improvement after treatment (relative risk [RR] = 0.70; 95% CI: 0.53-0.92). However, the main limitation of this SR and meta-analysis was the absence of a common objective outcome measure to evaluate effectiveness.

4.2.4.3.2.3.1 Summary of evidence and recommendations for urethral bulking agents

Summary of evidence	**LE**
Urethral bulking agents may provide short-term improvement and cure in women with SUI.	1b
Bulking agents are less effective than MUS, Burch colposuspension or autologous sling for cure of SUI and repeat injections may be required in order to achieve sustained benefits.	1b
Autologous fat and hyaluronic acid as bulking agents have a higher risk of adverse events.	1a
Adverse event rates for urethral bulking agents are lower compared to open surgery.	2a
There is no evidence that one type of bulking agent is better than another.	1b
The peri-urethral route of injection of bulking agents may be associated with a higher risk of urinary retention compared to the transurethral route.	2b

Recommendations	**Strength rating**
Offer urethral bulking agents to women seeking surgical treatment for stress urinary incontinence (SUI) following a thorough discussion of the risks and benefits relative to other surgical modalities.	Strong
Offer urethral bulking agents to women with SUI who request a low-risk procedure with the understanding that efficacy is lower than other surgical procedures, repeat injections are likely, and long-term durability and safety are not established.	Strong
Do not offer autologous fat and hyaluronic acid as urethral bulking agents due to the higher risk of adverse events.	Strong

4.2.4.3.2.4 Laser treatment
A SR including sixteen published studies, involving 899 patients with SUI, evaluated effects of laser treatment. The change in the ICIQ-SF score at one, two, and six months was -5.49, -4.97, and -5.48, respectively. The improvement in a 1-hour pad weight test results at one, three-, and twelve-months post treatment was -5.59, -4.96, and -5.82, respectively. The Pelvic organ prolapse/UI sexual questionnaire (PISQ-12) score increased by 5.39 (95% CI: 1.20-9.58) following treatment. Subgroup analysis identified the type and severity of UI as the potential source of heterogeneity. Adverse effects were reported in six of the sixteen trials and affected only a small number of patients. Most adverse events were mild or moderate and required no medical intervention or

resolved in a few days. According to this SR, vaginal laser therapy appears to be a safe, effective, and minimally-invasive treatment option for SUI that can be well tolerated by patients [383].

Another SR including 31 studies and 1,530 women confirmed that laser therapy seems to have a beneficial effect on prolapse and UI, but the level of evidence remains low without any suggestion on the laser type to be used, furthermore no studies are available on cost-effectiveness, in particular looking at a longer-term perspective, because surgical results may have more longevity than laser treatment, which may require re-application [384].

Another SR including a total of 27 studies, evaluated the effects of Er:YAG and Fractional CO_2 lasers. The overall quality of studies was poor, and 23/27 studies were case series (LE:4). Er:YAG laser showed a modest reduction in mild SUI cases, with benefits lasting a maximum of thirteen to sixteen months. Fractional CO_2 laser showed an improvement of mild SUI in few studies; however, no long-term data are available. When reported, adverse events were insignificant, however, they were not reported systematically [260]. A randomised double-blinded sham-controlled study in women with SUI [385] showed a significant reduction in the ICIQ-UI-SF after Er:YAG laser therapy vs. sham manipulated. However, only 21% were subjectively dry (ICIQ-SF = 0) vs. 4% of sham-operated women.

Overall, several limitations have been noted in the current literature regarding vaginal lasers, including variation in laser settings and protocols, short term follow-up, lack of urodynamic evaluation, and poor reporting of appropriate objective measures and adverse events. Based on the available literature, lasers cannot currently be recommended as a treatment option for SUI.

4.2.4.3.2.4.1 Summary of evidence and recommendations for laser treatment

Summary of evidence	**LE**
Several limitations have been noted in the current literature regarding vaginal laser treatment for SUI. These include variation in laser settings and protocols, short term follow-up, lack of urodynamic evaluation, and poor reporting of appropriate objective measures and adverse events.	1b

Recommendations	**Strength rating**
Do not offer vaginal laser therapy to treat stress urinary incontinence symptoms outside of a well-regulated clinical research trial.	Strong

4.2.4.3.2.5 Mid-urethral slings

Early clinical studies identified that non-autologous synthetic slings should be made from monofilament, nonabsorbable material, typically polypropylene, constructed as a 1–2 cm-wide mesh with a large pore size (macroporous) and coloured to facilitate removal [386]. Mid-urethral slings are now the most frequently used surgical intervention in Europe for women with SUI.

Transobturator route versus retropubic route

A Cochrane meta-analysis of MUS procedures for SUI in women was performed in 2017, spanning January 1947 to June 2014 [387]. Moderate-quality evidence from 55 studies showed variable, but comparable, subjective cure rates between retropubic (71–97%) and transobturator (62–98%) slings in the short term (up to one year). No difference in the objective cure rate in the short term was found. However, the ESTER SR [359], based on a network meta-analysis including 36 trials of overall moderate quality, showed that at twelve months retropubic MUS was more effective than transobturator MUS (OR: 0.74). The SUCRA scores for women cured after retropubic MUS were 89.1% vs. 64.1% after transobturator MUS. However, there was no significant difference in these cure rates between the two approaches. Similarly, based on 40 moderate-quality trials, retropubic MUS performed better than the transobturator approach in terms of symptom improvement (RR: 0.76) but the difference was, again, not significant.

Analysis of a randomised equivalence trial of retropubic vs. transobturator MUS for the treatment of SUI in women shows similar findings. This trial confirms equivalence of objective cure rates at twelve but not at 24 months (77.3% and 72.3% objective cure rate for retropubic and transobturator surgery). For both types of MUS, subjective and objective treatment success decreased over time and equivalence of the retropubic and the transobturator routes could not be confirmed at 24 and 60 months, with retropubic MUS demonstrating an increased benefit, despite satisfaction remaining high in both arms [388]. Five years after surgical treatment,

objective success was 7.9% greater in women assigned to retropubic sling compared to transobturator sling (51.3% vs. 43.4%), not meeting prespecified criteria for equivalence. Patient satisfaction decreased over five years but remained high and similar between treatment arms (retropubic sling 79% vs. transobturator sling 85%) [389].

In terms of long-term complications, data are scant but in one study de novo OAB developed in 14% of patients at ten years post transobturator tension-free vaginal tape (TVT-O) [390]. In a multicentre prospective study of women undergoing TOT, failure of previous anti-incontinence procedures was the only predictor of recurrence of SUI [390].

A long-term cohort study of retropubic TVT showed an 89.9% objective cure rate and a 76.1% subjective cure rate at ten years. Overall, 82.6% of patients reported high satisfaction with surgery [391]. A long-term prospective study on transobturator sling showed that, at 145 months, the objective and subjective cure rates were 78.9% and 62.6%, respectively; with no significant deterioration in SUI cure rates over time [392]. Another long-term follow-up study of patients treated with TVT showed a sustained response with 95.3%, 97.6%, 97.0% and 87.2% of patients being cured or improved at five, seven, eleven and seventeen years, respectively [393]. The ESTER network meta-analysis based on cure and improvement suggested that, when comparing surgical treatments for SUI, retropubic MUS, transobturator MUS and traditional sling had the highest efficacy, but this ranking does not consider the complication profile of these techniques. The short- to medium-term adverse event data are sparse [359].

Several health economic analyses of MUS procedures have been published with conflicting results. In a review of 26 economic evaluations and on the basis of a cost–utility and value of information analysis over a ten-year period, the authors concluded that MUS remains among the most cost-effective approaches [360]. A primary economic evaluation of retropubic vs. transobturator tapes over a five-year time period suggested that the latter may be cost-effective and cost-saving compared to the standard TVT approach [394]. Conversely, the findings from the ESTER network meta-analysis stated that over a lifetime, retropubic MUS was, on average, the least costly and most effective surgery but the level of uncertainty in these analyses was high.

Insertion using a skin-to-vagina direction versus a vagina-to-skin direction

The Cochrane review on MUS for female SUI showed no difference in the short- and medium-term subjective cure rates in vagina-to-skin (inside-out) vs. skin-to-vagina (outside-in) approaches, based on moderate-quality evidence [395]. Voiding dysfunction seems to be more frequent in the vagina-to-skin (inside-out) transobturator tape (TOT) group, but this approach is associated with a lower frequency of vaginal perforations (RR: 0.25). Due to the low quality of the evidence, it is unclear whether the lower frequency of vaginal perforations with this approach is responsible for the lower rate of vaginal tape erosions. Likewise, a meta-analysis of RCTs demonstrated no significant difference in efficacy between outside-in and inside-out approaches, but vaginal perforations were, again, less frequent in the latter group (2.6% vs. 11.8%, OR: 0.21) [396]. The five-year data of a prospective, non-RCT of the two techniques showed a high objective success rate (82.6 vs. 82.5%, respectively) with no difference between the two approaches [397]. In a secondary analysis of the E-TOT study (a study of transobturator MUS in the treatment of women with urodynamic MUI), no difference in the patient-reported success rates was found between the vagina-to-skin (inside-out) and the skin-to-vagina (outside-in) groups (63.2% and 65.5%, respectively; OR: 1.11) at nine years follow-up [398].

Complications of synthetic mid-urethral slings

The ESTER network meta-analysis noted that comparative assessment of adverse events between different procedures was not always possible due to the lack of available data [359]. Direct comparisons using head-to-head meta-analyses were mainly carried out for retropubic MUS, transobturator MUS or single-incision slings. The authors did, however, comment that "For other intervention comparisons, the number of studies was generally small and the CIs wide. However, there was some evidence to suggest that bladder perforation was more likely to occur after retropubic MUS than after transobturator MUS, open colposuspension or traditional sling". In particular, the retropubic approach for MUS was associated with a significantly higher rate of bladder perforation than transobturator MUS was (5% vs. 0.2%). Regarding *de novo* voiding dysfunction, 36 studies compared transobturator MUS with retropubic MUS, favouring the former (OR: 0.51). For pain, it is worth noting that it was defined and measured in many different ways across individual trials and across Cochrane reviews. Some pain outcomes were categorised by location (e.g., suprapubic) or time (e.g., short, or long term). These discrepancies made it difficult to combine data from different studies. Data were available mainly for the comparison between retropubic and transobturator MUS and other surgical procedures. However, groin pain was more frequent after transobturator MUS than retropubic MUS (6.3% vs. 1.3%; OR: 3.80). Converse findings were reported for suprapubic pain, which was higher following TVT (1.2% vs. 4.0%; OR: 0.37). Visceral injury

(0.5% vs. 2.4% OR: 0.36), mean operating time, intraoperative blood loss and hospital stay were lower in the transobturator than retropubic MUS groups. The overall vaginal erosion risk was low and comparable in both groups [359].

The rate of tape/mesh exposure or extrusion between retropubic and transobturator MUS was similar (2.1% vs. 2.4%; OR: 1.10). The exact time points at which measurements occurred could not be derived from the Cochrane reviews but most studies were reported to have a short follow-up period (≤ 12 months), with only a few studies having ≥ 2 years' follow-up [359]. Repeat surgery for UI was more common in the transobturator group (RR = 8.79); however, the data are limited and of low quality.

A population-based study performed in Scotland in > 16,000 women with SUI showed a similar rate of complications between mesh and non-mesh surgery [399]. However, a recent study of > 92,000 patients followed in the UK National Health Service showed a significant (9.8%) rate of complications using a broader definition and following patients for a longer period [400]. The level of detail regarding the precise nature of complications in this paper was poor. These findings suggest that, as with any SUI surgery, MUS can be associated with complications and fully informed consent is mandatory.

In general, the available published evidence would suggest that MUS does not seem to be associated with significantly higher rates of morbidity and complications compared to other surgeries for SUI, such as open retropubic Burch colposuspension. Pelvic organ prolapse is more common after colposuspension while voiding dysfunction occurs more often after MUS [364]. The ESTER review has commented that the level of detail regarding short-to-medium adverse event data is poor for all SUI surgeries [359] and the Panel is aware of the recent findings from the Independent Medicines and Medical Devices Safety Review in the UK that has raised the possibility that the level of complications from synthetic MUS may be higher than the medical literature would suggest [357].

The ESTER SR included seven studies comparing reintervention after transobturator and retropubic MUS [359]. Pooled analysis of these studies showed wide CIs and considerable uncertainty around the estimated OR (twelve-month post-surgery: 1.37). At one to five years after the procedure, rates of repeat continence surgery were higher in women undergoing transobturator MUS (18.3%) compared with retropubic MUS (0.5%), although only two studies were available for the analysis. A similar trend was observed in studies with a longer follow-up period (> 5 years) but the pooled analysis of these studies showed wide CIs. For retropubic MUS surgery, the bottom-to-top route was 10% more efficacious than top-to-bottom in terms of subjective cure and it was associated with less voiding dysfunction, bladder perforations and vaginal erosion [359].

Single-incision mid-urethral slings

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 operation. It should also be noted that some devices have been withdrawn from the market (e.g., TVT Secur®, Minitape, MiniArc®), and yet evidence relating to these devices may still be included in current meta-analyses. There is evidence to suggest that single-incision slings are quicker to perform and cause less postoperative thigh pain, but there is no difference in the rate of chronic pain. There is insufficient evidence for direct comparisons between single-incision slings, and no conclusions have been reached about differences between devices.

The ESTER SR showed, based on low-quality evidence, that at twelve months, retropubic and transobturator MUS were more effective than single-incision sling (TVT, OR: 0.50; TOT, OR: 0.68). The SUCRA score was 39.8% for women cured after single-incision slings. However, since not all single-incision devices have been assessed in a comparative RCT, it may be unsafe to assume that they are collectively technically similar or exhibit the same levels of efficacy.

A recent multicentre noninferiority RCT compared single-incision slings (Ajust® and Altis®) with conventional MUS during 36 months of follow-up, defining patient-reported success as a response of very much or much improved in the Patient Global Impression of Improvement questionnaire. After 36 months of follow-up success was reported by 177 of 246 patients (72.0%) and by 157 of 235 patients (66.8%) in the single-incision and MUS group, respectively. The authors conclude that single-incision slings were noninferior to standard MUS with respect to patient-reported success at fifteen months, and the percentage of patients reporting success remained similar in the two groups at 36-month follow-up [401].

Complications of single-incision slings
Meta-analysis of comparison between single-incision sling and transobturator MUS showed similar rates of mesh erosion or extrusion between interventions (4.8% vs. 3.7%; OR: 1.23). Rates of postoperative pain were higher after retropubic MUS than after single-incision slings (19.2% vs. 6.8%; OR: 0.21).

A noninferior RCT showed at 36 months a percentage of patients with groin or thigh pain of 14.1% with single-incision slings and 14.9% with MUS. Over the 36-month follow-up period, the percentage of patients with tape or mesh exposure was 3.3% with single-incision slings and 1.9% with MUS, and the percentage who underwent further surgery for SUI was 2.5% and 1.1%, respectively [401]. A multicentre single blind RCT compared postoperative pain scores and efficacy of a single-incision sling (Ajust®, n = 100) and a standard TOT (n = 56). Immediate postoperative pain was significantly lower for single-incision sling group, but *de novo* dyspareunia was higher (38.5% vs. 25%, with no statistical difference). No differences were reported in the objective cure at twelve months (90% vs. 88%) [402].

The rate of unspecified pain was higher after transobturator MUS than after single-incision sling at twelve months (1.0% vs. 5.2%; OR: 0.24) and 24 months (1.4% vs. 10.4%; OR: 0.16). Single-incision sling was associated with more repeat surgery compared with transobturator MUS (5.1% vs. 2.9%; OR: 1.57). At > 3 years after the procedure, the repeat surgery rate was 10.3% for single-incision slings vs. 7.6% for transobturator MUS (OR: 1.42) [359].

Sexual function after synthetic mid-urethral sling surgery
A SR examining the effect of synthetic MUS on female sexual function suggested different and contradictory results between studies. More studies have shown an improvement, or no change, in sexual function because of a reduction in coital incontinence, anxiety and avoidance of sex. Dyspareunia was the most common cause of worsening of sexual function and the precise incidence is difficult to estimate as many studies did not report it [403]. A meta-analysis of outcome measures in trials of sling procedures suggests that single-incision slings are associated with a significantly higher improvement in sexual function, however conflicting evidence was seen, compared to standard MUS procedures [404]. A recent RCT comparing single-incision slings with MUS showed similar outcomes with respect to QoL and sexual function in the two groups, with the exception of dyspareunia. Among the 290 women responding to a validated questionnaire, dyspareunia was reported by 11.7% in the single-incision group and 4.8% in the MUS group [401].

4.2.4.3.2.5.1 Summary of evidence and recommendations for mid-urethral slings

Summary of evidence	**LE**
The retropubic MUS appears to provide better patient-reported subjective and objective cure of SUI, compared with colposuspension.	1a
Synthetic MUSs inserted by the transobturator or retropubic route provide equivalent patient-reported outcomes at one year.	1a
Synthetic MUSs inserted by the retropubic route have higher patient-reported cure rates in the longer term.	1b
Long-term analyses of MUS cohorts showed a sustained response beyond 10 years.	2b
The retropubic route of insertion, compared with the transobturator route, is associated with a higher intraoperative risk of bladder perforation and a higher rate of voiding dysfunction.	1a
The transobturator route of insertion is associated with a higher risk of groin pain than the retropubic route.	1a
Long-term analysis of MUS showed no difference in terms of efficacy for the skin-to-vagina (outside-in) compared to vagina-to-skin (inside-out) directions up to nine years.	2a
The top-to-bottom (inside-out) direction in the retropubic approach is associated with a higher risk of postoperative voiding dysfunction.	1b
The comparative efficacy of Ajust® and Altis® single-incision slings against conventional MUS at fifteen and 36 months is non-inferior.	1b
Operating times for insertion of single-incision MUSs are shorter than for standard retropubic slings.	1b
Blood loss and immediate postoperative pain are lower for insertion of single-incision slings compared with conventional MUS.	1b

The rate of mesh exposure, repeat SUI surgery and dyspareunia at 3 years is higher for single-incision slings (Ajust® and Alits®) compared to conventional MUS.	1b
There is no evidence that other adverse outcomes from surgery are more or less likely with single-incision slings than with conventional MUS.	1b
In women undergoing surgery for SUI, coital incontinence is likely to improve.	3
Overall, there is conflicting evidence regarding sexual function following SUI surgery.	1a

NB: Most evidence on single-incision slings is from studies using the tension-free vaginal tape secure device, and although this device is no longer available, it is, however, still included in many systematic reviews and meta-analyses.

Recommendations	**Strength rating**
Offer a mid-urethral sling (MUS) to women seeking surgical treatment for stress urinary incontinence following a thorough discussion of the risks and benefits relative to other surgical modalities.	Strong
Inform women that long-term outcomes from MUS inserted by the retropubic route are superior to those inserted via the transobturator route.	Strong
Inform women of the complications associated with MUS procedures and discuss all alternative treatments in the light of recent publicity surrounding surgical mesh.	Strong
Inform women who are being offered single-incision slings (Ajust® and Altis®), that short term efficacy appears equivalent compared to conventional MUS.	Strong
Inform women who are being offered a single-incision sling that long-term efficacy remains uncertain.	Strong

4.2.4.3.2.6 Other treatments for uncomplicated stress urinary incontinence

Intravesical balloon treatment has been explored for women with SUI. The Vesair® gas-filled intravesical balloon differs from other treatment methods in that it is not intended to increase outlet resistance or minimise urethral hypermobility but to attenuate the fluctuation of intravesical pressure when the abdominal pressure increases [405, 406]. Two sham controlled RCTs have evaluated the Vesair® intravesical balloon [405, 407]. Both reported significant reductions in incontinence symptoms and pad weight, but QoL was not significantly different between study arms. High levels of adverse events were reported in both trials as well as significant numbers of withdrawals/device removals. The most common adverse events were dysuria, urgency, gross haematuria and UTIs.

Mechanical devices have been used to treat SUI for centuries. There are several devices available which act either by supporting the bladder neck or urethra to address urethral hypermobility, or by occluding the urethral lumen. A Cochrane review of eight RCTs that included three small trials comparing mechanical devices to no treatment found inconclusive evidence of benefit [408]. Another SR of mechanical devices concluded that there was insufficient evidence to support their use in women [409]. The place of mechanical devices in the management of SUI remains in question. Currently, there is little evidence from controlled trials on which to judge whether their use is better than no treatment, and large well-conducted trials are required for clarification. There is also insufficient evidence in favour of one particular device and few comparisons of mechanical devices with other forms of treatment [408].

Systematic reviews support the use of compression devices such as the adjustable compression therapy and artificial urinary sphincter (AUS) devices [410, 411]. Although these procedures are largely reserved for those with recurrent or complicated SUI (see Section 4.2.4.3.3.3 External compression devices), these recent additions to the literature include the use of some compression devices for uncomplicated SUI.

4.2.4.3.2.6.1 Summary of evidence and recommendations for other treatments for uncomplicated stress urinary incontinence

Summary of evidence	**LE**
Implantation of an artificial sphincter can improve or cure incontinence in women with uncomplicated SUI.	3
Implantation of the adjustable compression therapy (ACT®) device may improve uncomplicated SUI.	3
Complications, mechanical failure and device explantation often occur with both the artificial sphincter and ACT©.	3

Recommendations	Strength rating
Offer mechanical devices to women with mild-to-moderate SUI who fail conservative treatment only as part of a well-conducted research trial.	Strong
Inform women receiving artificial urinary sphincter or adjustable compression device (ACT®) that, although cure is possible, even in expert centres there is a high risk of complications, mechanical failure, or a need for explantation.	Strong

4.2.4.3.3 Surgery for women with complicated stress urinary incontinence

This section addresses surgical treatment for women with complicated SUI as defined in Section 4.2.2.

Women with associated genitourinary prolapse are included in Section 4.7.

The principal procedures included are:

- Colposuspension or MUS (synthetic or autologous) following failed primary SUI surgery;
- External compression devices: adjustable compression therapy (ACT®) and AUS;
- Adjustable slings.

4.2.4.3.3.1 Colposuspension or mid-urethral sling (synthetic or autologous) following failed primary stress urinary incontinence surgery

Urinary incontinence following SUI surgery may indicate persistent or recurrent SUI, or the development of *de novo* UUI, or both. Careful evaluation including urodynamics is an essential part of the work-up of these patients.

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 are usually too small to allow meaningful comparisons. This means that no firm recommendations can be made regarding which modality is best for the treatment of recurrent SUI, and previous SRs have commented that in view of the absence of any evidence, clinicians must rely largely on expert opinion or personal experience when advising patients about treatment options [412].

The ESTER network meta-analysis revealed that women with transobturator MUS were more likely to undergo repeat surgery than those who had retropubic MUS, and fewer repeat operations were observed after retropubic MUS compared with other interventions [359]. A recent update of two Urinary Incontinence Treatment Network trials [413] compared the retreatment-free survival rates by initial surgical procedure. Five-year retreatment-free survival rates were 87%, 96%, 97%, and 99% for Burch colposuspension, autologous fascial sling, transobturator, and retropubic MUS, respectively. Types of surgical retreatment included autologous fascial sling (19), bulking agent (18), and synthetic sling (1). This suggests that MUS may not be preferred in cases of recurrent SUI [413].

In these cohorts, 6% of women after standard anti-incontinence procedures were retreated within five years, mostly with injection therapy or autologous fascial sling. Not all women with recurrent SUI chose surgical retreatment.

A Cochrane review attempted to summarise the data regarding different types of MUS procedures for recurrent SUI after failure of primary surgical therapy [414]. The literature search identified 58 records, but all were excluded from quantitative analysis because they did not meet eligibility criteria. Overall, there were no data to recommend or refute any of the different management strategies for recurrent or persistent SUI after failed MUS surgery. Another SR looking at the effectiveness of MUS in recurrent SUI included twelve studies and reported an overall subjective cure rate following MUS for recurrent SUI after any previous surgery of 78.5% at an average 29 months' follow-up [415]. The subjective cure rate following MUS after previous failed MUS was 73.3% at follow-up of sixteen months. The authors commented that there was a lower cure rate with transobturator compared to the retropubic tape for recurrent SUI after previous surgery. Conflicting evidence comes from a SR assessing the effectiveness and complications of various surgical procedures for female recurrent SUI and reported on data from 350 women in ten RCTs with a mean follow-up of 18.1 months [416]. The authors found no difference in patient-reported and objective cure/improvement rates between retropubic and transobturator MUS in the setting of recurrent SUI. There was also no significant difference between Burch colposuspension and retropubic MUS in terms of patient-reported improvement or objective cure/improvement.

A SR of older trials of open surgery for SUI suggested that the longer-term outcomes of repeat open Burch colposuspension may be poor compared to autologous fascial slings [417]. Similarly, one large non-randomised comparative series suggested that cure rates after more than two previous operations were 0% for open Burch colposuspension and 38% for autologous fascial sling [418].

4.2.4.3.3.1.1 Summary of evidence for surgery in those with recurrent stress urinary incontinence following failed primary surgery

Summary of evidence	LE
Failure rates of single-incision slings appear higher than with other types of MUS.	1a
The incidence of repeat surgery is higher in those women who underwent primary transobturator compared to retropubic MUS.	1a
The five-year failure rate of Burch colposuspension appears higher than for synthetic or traditional sling procedures.	2b
Some studies suggest that retropubic synthetic MUS procedures appear to be more effective than transobturator MUS for the treatment of recurrent SUI, but this is not a consistent finding in the literature.	1a
Most procedures are less effective when used as second-line procedures.	2a
Burch colposuspension has similar short-term patient-reported or objective cure rates when compared to TVT for treatment of recurrent SUI.	1b
Autologous sling appears superior to Burch colposuspension for treatment of recurrent SUI.	2b

4.2.4.3.3.2 Adjustable slings

Although adjustable slings are most commonly used for treatment of complicated SUI, they may also be considered for uncomplicated SUI. There are no RCTs investigating outcome of adjustable sling insertion for women with SUI. There are limited data from cohort studies on adjustable tension slings with variable selection criteria and outcome definitions. Few studies have included sufficient numbers of patients or have long enough follow-up to provide useful evidence.

One adjustable sling is the Remeex system (Neomedic International®, Terrassa, Spain), which was investigated in a prospective study of 230 women with SUI [419]. After a mean follow-up of 89 months, 165 patients were cured of SUI (71.7% in the intention-to-treat [ITT] analysis, 80.5% in per protocol [PP] analysis). Forty patients remained incontinent (17.4% in ITT, 19.5% in PP) and 88 patients required readjustment of the sling during follow-up.

The tension was increased in 82 cases due to recurrence of SUI and reduced in six due to outlet obstruction. The currently available adjustable sling devices have differing designs, making it difficult to draw general conclusions about them as a class of procedure.

4.2.4.3.3.2.1 Summary of evidence for adjustable slings

Summary of evidence	LE
There is only low-level evidence to suggest that adjustable MUS devices may be effective for cure or improvement of SUI in women.	3
There is no evidence that adjustable slings are superior to standard MUS.	4

4.2.4.3.3.3 External compression devices

External compression devices are usually used for treatment of recurrent SUI after failure of previous surgery but can be considered for primary treatment. Studies have largely included patients with profound intrinsic failure of the sphincter mechanism, characterised by low VLPP or urethral closure pressure [410, 411]. The two intracorporeal external urethral compression devices available are the adjustable compression therapy (ACT®) device and AUS.

ACT®: Using US or fluoroscopic guidance, the ACT® device is inserted by placement of two inflatable spherical balloons; one on either side of the bladder neck. The volume of each balloon can be adjusted through a subcutaneous port placed within the labia majora. A SR including eight studies published between 2007 and 2013 with follow-up of one to six years revealed 15–44% of patients considered that their SUI had been cured and 66–78.4% were satisfied [410]. The explantation rate was 19–31%. In these studies, a significant reduction in the number of pads used daily was consistently observed after ACT® balloon placement and QoL was significantly improved. The authors concluded that ACT® balloons constitute a reasonable, minimally-invasive alternative for treatment of female SUI due to intrinsic sphincter deficiency, especially in patients who have already experienced failure of standard surgical treatment.

AUS: The major advantage of AUS over other anti-incontinence procedures is the perceived ability to be able to void normally [408]. There have been a few case series of AUS in women, with populations of 45–215 patients and follow-up of one month to 25 years [420-423]. 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 cure in 59–88%. Common adverse effects included mechanical failure requiring revision (≤ 42% at ten years) and explantation (5.9–15%). In a retrospective series of 215 women followed-up for a mean six years, the risk factors for failure were older age, previous Burch colposuspension and pelvic radiotherapy [423].

Early reports of laparoscopically implanted AUS do not have sufficient patient populations or sufficient follow-up to be able to draw any conclusions [424, 425].

A more recent SR included seventeen studies, but all were retrospective or prospective non-comparative case series [411]. Most patients had undergone at least one anti-incontinence surgical procedure prior to AUS implantation (69.1–100%). Outcomes revealed that complete continence rates were 61–100%. The rates of explantation were 0–45%, erosion rates were 0–22% and mechanical failure rates were 0–44%. The authors concluded that AUS can provide excellent functional outcomes in women with SUI resulting from intrinsic urethral sphincter deficiency but at the cost of high morbidity.

4.2.4.3.3.3.1 Summary of evidence for external compression devices

Summary of evidence	LE
Implantation of an artificial sphincter improves or cures incontinence in women with SUI caused by sphincter insufficiency.	3
Implantation of the AUS device may improve complicated SUI.	3
Implantation of the ACT® device may improve complicated SUI.	3
Complications, mechanical failure, and device explantation often occur with both the artificial sphincter and ACT®.	3
Explantation of AUS is more frequent in older women and among those who have had previous Burch colposuspension or pelvic radiotherapy.	3

4.2.4.3.3.4 Recommendations for complicated stress urinary incontinence

Recommendations	Strength rating
Management of complicated stress urinary incontinence (SUI) should only be offered in centres with appropriate experience (see Section: 4.2.4.3.1).	Strong
Base the choice of surgery for recurrent SUI on careful evaluation, including individual patient factors and considering further investigations such as cystoscopy, multichannel urodynamics, as appropriate.	Strong
Inform women with recurrent SUI that the outcome of a surgical procedure, when used as second-line treatment, is generally inferior to its use as first-line treatment, both in terms of reduced efficacy and increased risk of complications.	Weak
Only offer adjustable mid-urethral sling as primary surgical treatment for SUI as part of a structured research programme.	Strong
Consider secondary synthetic sling, bulking agents, Burch colposuspension, autologous sling or artificial urinary sphincter (AUS) as options for women with complicated SUI.	Weak
Inform women receiving AUS or ACT® device that, although cure is possible, even in expert centres, there is a high risk of complications, mechanical failure, or a need for explantation.	Strong

4.2.4.3.4 Surgery for stress urinary incontinence in special patient groups

4.2.4.3.4.1 Stress urinary incontinence surgery in obese women

There is no agreement about the outcome of incontinence surgery in obese women. Secondary analysis of an RCT on retropubic and transobturator tapes for treatment of women with SUI suggests that obese women experience inferior outcome compared to non-obese women. Stratification of patients according to BMI (< 30 and > 30) shows a significant difference in objective dry rates (negative pad test) at one year (85.6% vs. 67.8%) and five years (87.4% vs. 65.9%) and subjective cure (absence of SUI symptoms) at one year (85.8% vs. 70.7%) and five years

(76.7% vs. 53.6%). At one and five years, 6.7% and 16.3% of patients who were initially dry (negative pad test) after surgery developed a positive pad test [426, 427].

Conversely, short-term outcome of single-incision MiniArc® sling showed comparable objective cure rates (negative cough stress test) at two years (86% and 81% in non-obese and obese women, respectively); similar improvement of the Urinary Distress Inventory six and Incontinence Impact Questionnaire seven was observed in non-obese and obese women [428]. Objective cure rate was also similar with Altis® (88% and 87% in non-obese and obese women) at two years follow-up [429].

4.2.4.3.4.2 Stress urinary incontinence surgery in elderly women

Age appears to be a significant factor in outcome from SUI surgery but there is conflicting evidence. 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 years [430]. An RCT assessing risk factors for the failure of TVT vs. TVT-O in 162 women also found that age was a specific risk factor for recurrence at one year [431]. In addition, based on a sub-analysis of a trial cohort of 655 women at two years' follow-up, it was shown that elderly women were more likely to have a positive stress test at follow-up, were less likely to report objective or subjective improvement in stress and UUI, and were more likely to undergo retreatment for SUI. There was no difference in time to postoperative normal voiding [432].

Another RCT comparing immediate TVT vs. no surgery (or delayed TVT) in older women, confirmed efficacy of surgery in terms of QoL and satisfaction, but with more complications in the surgical arm [433].

Furthermore, a SR of the efficacy of treatments of UI in older patients suggests that MUS is successful in older patients (≥ 65 years) with 5.2–17.6% reporting persistent SUI after surgery. No difference in the frequency of *de novo* UUI, persistent UUI or persistent SUI was found in older patients [361].

4.2.4.3.4.3 Summary of evidence and recommendations for stress urinary incontinence surgery in special patient groups

Summary of evidence	LE
Incontinence surgery may be safely performed in obese women; however, outcomes may be inferior.	1
The risk of failure from surgical repair of SUI, and the risk of adverse events, appears to increase with age.	2b
There is no evidence that any surgical procedure has greater efficacy or safety in older women than another procedure.	4

Recommendations	Strength rating
Inform obese women with stress urinary incontinence (SUI) about the increased risks associated with surgery, together with the lower probability of benefit.	Weak
Inform older women with SUI about the increased risks associated with surgery, together with the likelihood of lower probability of benefit.	Weak

4.2.5 Follow-up

The follow-up of patients with SUI is dependent on the treatment given. For conservative and physical therapies, sufficient time should be allowed for the demonstration of a therapeutic effect. For pharmacological treatment, early follow-up is recommended. For most surgical interventions, short-term follow-up should be arranged to assess efficacy and identify any early postoperative complications.

The Panel is supportive of long-term outcome assessment via registries and recognises the paucity of high-quality long-term data, specifically regarding complications from surgery.

4.3 Mixed urinary incontinence

The term MUI is broad because it may refer to equal stress and urgency symptoms, stress-predominant symptoms, urgency-predominant symptoms, urodynamic stress urinary incontinence (USUI or USI) with DO or USUI with clinical urgency symptoms, but no DO [434]. The challenge of this broad definition is that it leads to inconsistencies when evaluating treatment options and outcomes.

4.3.1 Epidemiology, aetiology and pathophysiology

The prevalence rates of MUI vary widely in the literature. Most epidemiological studies have either not considered subtypes of UI, or only reported on SUI, UUI and MUI. The current literature is unclear regarding the population prevalence and risks for the different UI subtypes [435]. There are many urinary symptom questionnaires used in epidemiological research, with varying evidence of validity. Caution is needed when comparing epidemiological studies that do or do not report a separate MUI subgroup, and when generalising from population level data to clinical practice. The problems arise from significant heterogeneity in terms of types of questionnaires/surveys used, population parameters, variable response rates, varying definitions of MUI, and outcome measures.

It seems apparent, however, that MUI is the second most common form of UI, after SUI, with most studies reporting a 7.5–25% prevalence [435]. One can extrapolate that among women with UI, approximately one-third have MUI [436]. In a secondary analysis of a large clinical trial, 655 women were evaluated for UI and their response to treatment [437]. It was found that 50–90% of women fell into the category of MUI based on patient-reported answers to the Medical Epidemiologic and Social Aspects of Aging and Urinary Distress Inventory (UDI) questionnaires. However, when objective criteria such as urodynamic findings were used, only 8% of women were categorised as having MUI.

Mixed urinary incontinence is usually caused by a combination of the same factors that cause SUI and UUI. Several factors may be responsible for its development, including oestrogen deficiency, abnormalities in histomorphology, and microstructural changes [438]. One report postulates that an incompetent sphincter and bladder neck allow urine to enter the proximal urethra during stress, causing a urethro-detrusor reflex that triggers involuntary detrusor contraction, which then causes urgency and UUI [439]. Another study has shown that urine flow across the urethral mucosa increases the excitability of the micturition reflex [440]. Ultimately, it is unlikely that one theory or risk factor can explain the development of MUI and its symptoms; it is more probable that disturbances in several elements and the lack of bladder compensation results in the development of MUI [438].

4.3.2 Diagnostic evaluation

Assessment of patients with MUI begins with a thorough history of the patient's urinary symptoms and follows the recommendations set out in the general evaluation and diagnosis of LUTS in Chapter 3. It is conventional to try and categorise MUI as either stress or urge predominant.

Mixed urinary incontinence is difficult to diagnose, as the condition comprises many phenotypes. Some women exhibit detrusor contractions provoked by physical stressors, some have unprovoked detrusor contractions, and many have no abnormal detrusor contractions, but still report urine leakage with the sensation of urgency. Some women with urgency symptoms do not manifest UUI because their urethral sphincter is strong and often able to prevent urine leakage [441].

The role of urodynamics in MUI is unclear but establishing objective degrees of SUI and DO incontinence may help in counselling patients about the most appropriate initial treatment option.

4.3.2.1 Summary of evidence and recommendations for the diagnosis of mixed urinary incontinence

Summary of evidence	**LE**
There is no evidence that urodynamics affects outcomes of treatment for MUI.	3

Recommendations	**Strength rating**
Complete a thorough history and examination as part of the assessment of mixed urinary incontinence (MUI).	Strong
Characterise MUI as either stress-predominant or urgency-predominant where possible.	Weak
Use bladder diaries and urodynamics as part of the multimodal assessment of MUI to help inform the most appropriate management strategy.	Strong

*4.3.3 **Disease management***

4.3.3.1 Conservative management

Women with MUI generally have more severe symptoms and respond less well to treatment than women with only SUI or UUI [442]. Clinicians are encouraged to begin treatment for MUI with conservative management directed toward the most bothersome component of the symptom spectrum and to reserve surgery as a last resort [441].

4.3.3.1.1 Pelvic floor muscle training

An RCT comparing PFMT with and without an audiotape for 71 women with UI did not find any difference between the two treatment arms [443]. Mean number of incontinent episodes per day decreased from 3.9 overall to 3.2 for participants with MUI. Six months after completing the course of exercises, approximately one third of all enrolees reported that they continued to note good or excellent improvement and desired no further treatment.

A small RCT including 34 women with SUI and MUI compared eight weeks of PFMT with no treatment and found that PFMT significantly increased PFM strength, improving QoL, and reduced the frequency of UI episodes compared to no treatment [444]. Another RCT including SUI and MUI confirmed these results [445].

A multicentre randomised controlled non-inferiority trial on 467 women with MUI was conducted in ten hospitals. Participants were randomised 1:1 to receive EA (36 sessions over twelve weeks with 24 weeks of follow-up) or PFMT–solifenacin (5 mg/day) over 36 weeks. In women with moderate-to-severe MUI, EA was not inferior to PFMT–solifenacin in decreasing the 72-hour incontinence episodes (between-group difference, –1.34%) [446].

In a comparative study of the effectiveness of behavioural therapy and PFMT (combined with MUS vs. sling alone in women with MUI), 416 (86.7%) had post-baseline outcome data and were included in the primary twelve-month analyses [447]. The UDI score in both groups significantly decreased (178.0 to 30.7 points in the combined group, 176.8 to 34.5 points in the sling-only group). The model estimated between-group difference, did not meet the minimal clinically important difference threshold. Adherence to the behavioural therapy and PFMT regimes, which is a prerequisite for achieving a satisfactory outcome, was not reported in the study.

A Cochrane review comparing PFMT with no or sham treatment included 31 RCTs from fourteen countries, but there was only one study including women with MUI and one with UUI and none of them reported data on cure, improvement, or number of episodes of these subgroups [316].

The effect of combining biofeedback with PFMT has already been fully addressed in Section 4.2.4.1.3, and there was no evidence of any additional benefit in a population with predominantly MUI.

4.3.3.1.2 Bladder training

Details on BT programmes are given in Section 4.2.4. The ICI 2017 [322] concluded that for women with UUI or MUI, PFMT and BT are effective first-line conservative therapies. One RCT assigned 108 women with diagnoses of SUI (n = 50), UUI (n = 16), or MUI (n = 42) to six weeks of BT and PFMT or BT alone [448]. Overall, and in the SUI and MUI subgroups, significantly more patients in the BT and PFMT group reported cure and improved symptoms.

4.3.3.1.3 Electrical stimulation

A Cochrane review on ES for SUI included participants with SUI or stress-predominant MUI. Twenty-five percent of the included trials were deemed to have a high risk of bias due to a variety of factors, including baseline differences between groups and industry funding. For subjective cure or improvement of SUI, low-quality evidence indicated that ES was better than no active treatment or sham treatment. Electrical stimulation for OAB and SUI is covered in Sections 4.1.4.1.5.4 and 4.2.4.1.3.2.

4.3.3.2 Summary of evidence and recommendations for conservative management in mixed urinary incontinence

Summary of evidence	**LE**
Pelvic floor muscle training appears less effective for MUI than for SUI alone.	2
Pelvic floor muscle training is better than no treatment for improving UI and QoL in women with MUI.	1a
Bladder training combined with PFMT may be beneficial in the treatment of MUI.	1b

Recommendations	Strength rating
Treat the most bothersome symptom first in patients with mixed urinary incontinence (MUI).	Weak
Offer bladder training as a first-line therapy to adults with MUI.	Strong
Offer supervised intensive pelvic floor muscle training, lasting at least three months, as a first-line therapy to all women with MUI (including elderly and postnatal women).	Strong

4.3.3.3 Pharmacological management

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.

4.3.3.3.1 Anticholinergics

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 [449]. In another study (n = 1,380) tolterodine was equally effective in reducing urgency and UUI symptoms, regardless of whether there was associated SUI [450]. Similar results were found for solifenacin [451, 452].

4.3.3.3.2 Duloxetine

In one RCT of duloxetine vs. placebo, 588 women were stratified into either stress-predominant, urgency-predominant or balanced MUI groups. Duloxetine was effective for improvement of incontinence and QoL in all subgroups, although results in the stress-predominant groups were better [453]. Treatment-emergent adverse event rate in the duloxetine group was 61.3% with discontinuation rates of 15.7%. Adverse event rates were higher in those participants taking other concomitant antidepressant agents.

Duloxetine was found to have equal efficacy for SUI and MUI in an RCT (n = 553) following secondary analysis of respective subpopulations, but no adverse events data were reported [454].

4.3.3.3.3 Summary of evidence and recommendations for pharmacological management of mixed urinary incontinence

Summary of evidence	LE
Limited evidence suggests that anticholinergic drugs are effective for improvement of the UUI component in patients with MUI.	2
Duloxetine is effective for improvement of both SUI and MUI symptoms, but adverse event rates are high.	1b

Recommendations	Strength rating
Treat the most bothersome symptom first in patients with mixed urinary incontinence (MUI).	Weak
Offer anticholinergic drugs or beta-3 agonists to patients with urgency-predominant MUI.	Strong
Offer duloxetine (where licensed) to selected patients with stress-predominant MUI unresponsive to other conservative treatments and who want to avoid invasive treatment, counselling carefully about the risk of adverse events.	Weak

4.3.3.4 Surgical management

The surgical treatment options for MUI, include all the anti-incontinence procedures as outlined in the SUI Section 4.2.4.3.

Many RCTs include patients with pure SUI or pure UUI as well as patients with MUI. However, few RCTs report separate outcomes for MUI subgroups.

Post hoc analysis of a large RCT showed that in women undergoing either autologous fascial sling or Burch colposuspension, the outcomes were poorer for women with a concomitant complaint of preoperative urgency [432]. A similar post hoc review of another RCT comparing transobturator and retropubic MUS showed that the greater the severity of preoperative urgency, the more likely that treatment would fail [98]. 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). Another RCT including 93 patients with MUI showed a significant improvement in continence and QoL in the group that had TVT and botulinum toxin A (Botox®) rather than with either treatment alone [455].

In a secondary analysis of a study of transobturator TVTs in the treatment of women with urodynamic MUI, no difference in patient-reported success rates was found between the vagina-to-skin (inside-out) and the skin-to vagina (outside-in) groups (63.2% and 65.5%, respectively) at nine years' follow-up [398].

Analysis of the trial populations included in the meta-analysis on single-incision slings suggests that the evidence can be generalised to women who have predominantly SUI, and no other clinically severe LUT 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.

Research trials should define accurately what is meant by MUI. 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.

4.3.3.4.1 Summary of evidence and recommendations for surgery in patients with mixed urinary incontinence

Summary of evidence	**LE**
Women with MUI are less likely to be cured of their UI by SUI surgery than women with SUI alone.	2
The response of pre-existing urgency symptoms to SUI surgery is unpredictable.	1b

Recommendations	**Strength rating**
Treat the most bothersome symptom first in patients with mixed urinary incontinence (MUI).	Weak
Warn women that surgery for MUI is less likely to be successful than surgery for stress urinary incontinence alone.	Strong
Inform women with MUI that one single treatment may not cure urinary incontinence; it may be necessary to treat other components of the incontinence problem as well as the most bothersome symptom.	Weak

4.4 Underactive bladder

Underactive bladder is a common clinical entity, defined by the ICS as "a symptom complex characterised by a slow urinary stream, hesitancy, and straining to void, with or without a feeling of incomplete bladder emptying sometimes with storage symptoms" [456]. Diagnosis of UAB is based on clinical symptoms and the presentation and aetiology can be variable.

This differs from DU, which is a diagnosis based on urodynamic studies. Detrusor underactivity is defined by the ICS as "*a detrusor contraction of reduced strength and/or duration, resulting in prolonged bladder emptying and/or failure to achieve complete bladder emptying within a normal time span*" [1]. Acontractile detrusor is specified when there is no measurable detrusor contraction.

Female voiding dysfunction is defined by the ICS as "*a diagnosis based on symptoms and urodynamic investigations characterised by abnormally slow and/or incomplete micturition, based on abnormally slow urine flow rates and/or abnormally high PVR volume*" [113]; ideally on repeated measurement to confirm abnormality. Pressure–flow studies may be required to determine the precise cause of the voiding dysfunction [31].

*4.4.1 **Epidemiology, aetiology, pathophysiology***

4.4.1.1 Epidemiology

Underactive bladder as an entity remains difficult to characterise, partly because its corresponding urodynamic correlate, DU, remains loosely defined, leading to significant variability in diagnostic criteria across research studies and significant overlap of symptoms with other conditions. As a consequence of the variable definition, reported prevalence also varies and ranges from 12-45% in women, with increased prevalence seen with age [75] and in institutionalised elderly women [457].

Several studies have demonstrated similar prevalence rates for DU in the ambulatory setting of around 12–19% [458-460]. As would be expected, voiding symptoms consistent with UAB are higher. In a large cross-sectional, population-based internet survey conducted in the USA, UK and Sweden including 15,861 women aged ≥ 40 years, 20.1% had weak flow, 27.4% had incomplete bladder emptying and 38.3% had terminal dribbling [5].

Both DO during filling and DU in the voiding phase of urodynamic studies can co-exist (formerly known as detrusor hyperactivity with impaired contractility [DHIC]) and one study showed the prevalence of this finding was over 30% in elderly women [457].

4.4.1.2 Aetiology

The presence of DU in diverse clinical groups suggests multifactorial aetiology [461]. Idiopathic DU is probably partly an age-dependent decrease in detrusor contractility with no other identifiable causes, but young women can also have DU. There are many secondary causes of DU, including neurogenic (e.g., multiple sclerosis, multiple systemic atrophy, spinal cord injury, spina bifida, Parkinson's disease, hydrocephalus, transverse myelitis, stroke, Guillain–Barré syndrome, diabetes mellitus, and pelvic nerve injury), myogenic (prolonged bladder overdistension, diabetes mellitus, and BOO) and iatrogenic (pelvic surgery) causes [462].

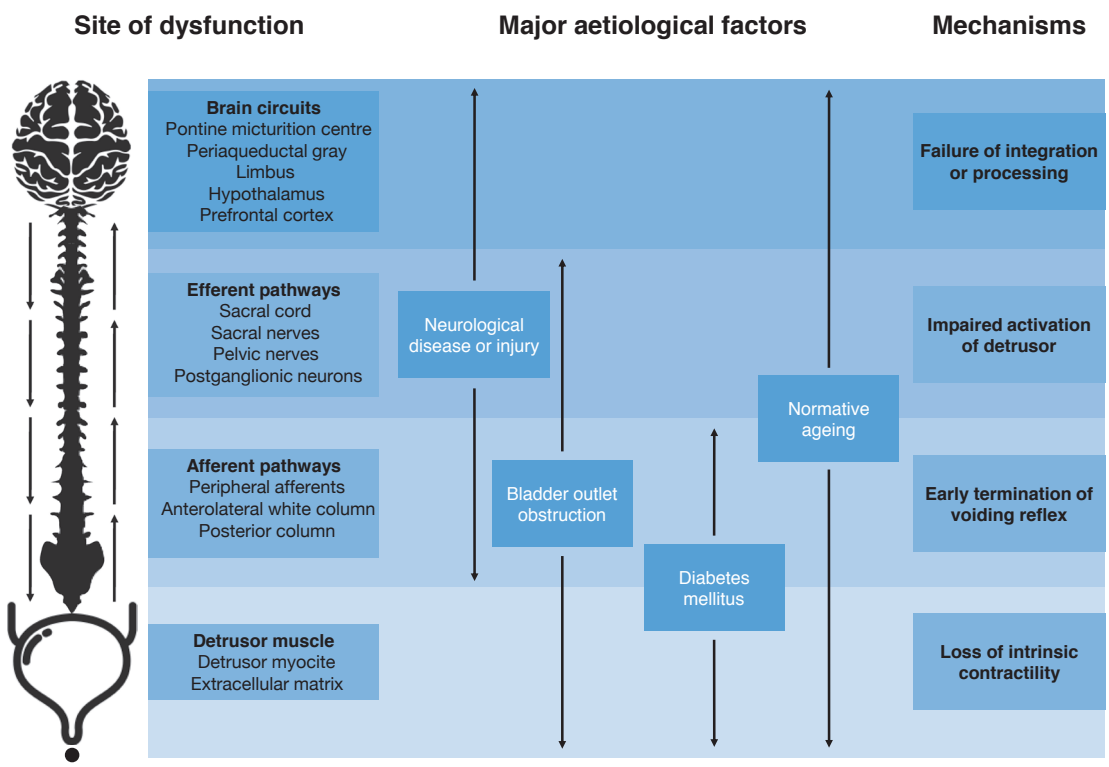
4.4.1.3 Pathophysiology

Many pathways are involved in normal detrusor contraction, and there are different possible sites of dysfunction [75] with a variety of mechanisms involved in UAB (see Figure 1):

- Central circuits and centres (prefrontal cortex, periaqueductal gray, pontine micturition centre and hypothalamus): failure of integration or processing.
- Efferent pathways (sacral cord, sacral nerves, pelvic nerves, and postganglionic neurons): impaired detrusor activation.
- Afferent pathways (peripheral afferent nerves, anterolateral white column, and posterior column): early termination of voiding reflex.
- Muscle (detrusor myocytes and extracellular matrix): loss of intrinsic contractility.

Different aetiologies can share common pathophysiological mechanisms: for example, diabetes mellitus affects mainly afferent pathways and the detrusor muscle; and neurogenic diseases affect central circuits and efferent/ afferent pathways.

Figure 1: Management and treatment of women presenting with urinary incontinence, site of dysfunction, major aetiological factors, mechanisms



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*4.4.2 **Classification***

There is no current classification system of UAB. Patients can be classified according to presumed aetiology or pathogenic mechanism, but without sufficient longitudinal data or high-level evidence to establish prognostic factors, the classification of UAB patients in terms of relevant clinical characteristics or risk of complications is not possible.

*4.4.3 **Diagnostic evaluation***

4.4.3.1 Symptoms associated with detrusor underactivity

A retrospective study correlated LUTS with urodynamic findings in 1,788 patients (1,281 women). Women with DU, defined as detrusor pressure at maximum flow rate (PdetQmax) < 20 cm H2O, maximum flow rate (Qmax) < 15 mL/s, BVE < 90% and no sign of obstruction on video-urodynamic studies, had a significantly higher occurrence of reduced and/or interrupted stream, hesitancy, feeling of incomplete bladder emptying, palpable bladder, and absent and/or decreased sensation compared with women with normal pressure and flow [463]. A qualitative study on a small sample of male and female patients diagnosed with DU reported a variety of LUTS and associated impact on QoL. Storage symptoms of nocturia, increased daytime frequency, and urgency, and the voiding symptoms of slow stream, hesitancy, and straining were reported by over half of the patients. A sensation of incomplete emptying and post-micturition dribble were also frequently described. The impact of their symptoms on QoL was variable, but in general, storage symptoms were more bothersome [464].

Based on current data, it is not possible to find a pivotal symptom or collection of symptoms to identify DU patients. The ICI Questionnaire-Underactive Bladder (ICIQ-UAB) has been developed as a research PROM tool [465].

4.4.3.2 Urodynamic studies

Non-invasive studies like uroflowmetry, PVR volume measurement and BVE determination are potentially useful to identify women who might have DU. There is considerable symptomatic overlap with BOO, and uroflowmetry and PVR volume findings may also be similar. Only invasive urodynamics with pressure–flow studies can reliably distinguish DU from BOO and these urodynamic diagnoses can coexist. Diagnosis in women is particularly difficult as they can void by relaxing the pelvic floor, that is, without detectable detrusor contraction during pressure–flow study and without increased abdominal pressure [466]. The simplest methods to define and diagnose DU are based on the use of cut-off values of Q_{max} and $P_{det}Q_{max}$, possibly combined with cut-off values of PVR volume and BVE. However, there is no consensus on which cut-off values should be used [467]. It is obvious that the prevalence of DU depends on the criteria used. In a retrospective study of 1,015 women, DU was found in 14.9% when using Q_{max} < 12 mL/s or PVR volume > 150 mL; in 9.6% when using $P_{det}Q_{max}$ < 30 cm H_2O and Q_{max} < 10 mL/s; and in 6.4% when using $P_{det}Q_{max}$ < 20 cm H_2O, Q_{max} < 15 mL/s and BVE < 90% [468].

More elaborate methods combine urodynamic data into an index or a physical quantity that reflects bladder contraction strength. A value below a certain threshold would thus diagnose DU. Again, there is no consensus regarding what is normal/abnormal. Table 4 provides an overview of the best-known parameters, their background, and typical values. Watt's factor (WF) estimates the power generated by the detrusor per unit area of bladder surface [469] and it varies during voiding. Usually, WF_{max} is considered. Alternatively, its value at Q_{max} can be used. Projected isovolumetric pressure (PIP) is a gross simplification of the bladder output relation and estimates the maximum detrusor pressure that can be generated by the bladder when the outlet is closed; the isovolumetric detrusor pressure. The bladder contractility index (BCI) is a reduction of PIP to an index [470]. The population in which PIP and BCI were developed mainly consisted of men. Projected isovolumetric pressure 1, is similar to PIP and also estimates the isovolumetric detrusor pressure, but was developed in an entirely female population via an experimental method [471].

A third method of quantifying bladder contraction strength involves stop tests. One study compared three types of direct measurement of isovolumetric pressure: (1) the voluntary stop test, in which the patient voluntarily interrupted flow; (2) the mechanical stop test, in which flow was interrupted by a balloon catheter; and (3) the continuous occlusion test, in which the subject tried to void against a blocked outlet. The latter had the best reliability and best detected drug-induced changes, though the results of the mechanical stop tests were similar [472].

All parameters discussed above give some information about the strength of detrusor contraction in a given void. They do not necessarily reflect what the detrusor might potentially achieve under optimum conditions [473]. Also, they give no information on voiding duration. No parameters for this are available. Finally, abnormally low bladder contraction strength does not necessarily imply insufficient bladder contraction strength to achieve optimal voiding. Table 4 summarises different parameters to measure detrusor contraction in female patients.

Table 4: Most used parameters to measure detrusor contraction in female patients

Parameter	Basis	Population	Values
Watt's factor [469]	Hill equation of muscle contraction in a spherical organ, with fixed constants obtained from experimental and clinical studies	Eight asymptomatic female volunteers aged 28–45 years (median 34 years)	Ideal voiding (bell-shaped flow curves): WF_{max} 11-24 W/m^2 Non-ideal voiding: WF_{max} 5–10 W/m^2 Normally WF_{max} > 7 W/m^2 (expert opinion, unspecified population) [474]
Projected isovolumetric pressure (cm H_2O) and BCI, using PIP as an index [470, 475]	Bladder output relation, simplified to a straight line with fixed slope of 5 cm H_2O/mL/s (formula: $P_{det}Q_{max} + 5xQ_{max}$)	Unspecified population, mainly men with BPO	Classification based on expert opinion: > 150: strong contraction 100–150: normal contraction 50–100: weak contraction < 50: very weak contraction
Projected isovolumetric pressure 1 (cm H_2O) [471]	Comparison of Q_{max} and $P_{det}Q_{max}$ values with stop test results (Formula: $p_{det}Q_{max} + Q_{max}$)	100 women with UUI aged 53–89 (mean 70) years	5^{th}-95^{th} percentile: 29–78 cm H_2O Mean: 49 cm H_2O Median: 48 cm H_2O Proposed typical values: 30-75 cm H_2O
Continuous occlusion test [472]	Direct measurement of isovolumetric voiding contraction	70 women with UUI aged 53–89 (mean: 70) years	Mean ± SD: 48.7 ± 24.4 cm H_2O

BCI = Bladder contractility index; PIP = Projected isovolumetric pressure; UUI = urgency urinary incontinence; WF = Watt's factor.

*4.4.4 **Disease management***

As there are different possible causes and pathogenic mechanisms involved in female UAB, preventive and therapeutic strategies are difficult to define. Among preventive strategies, early recognition after major surgery or labour might prevent long-term problems associated with prolonged bladder over-distension. Nerve-sparing techniques for radical pelvic surgery are more favourable in terms of early recovery of bladder function [476, 477].

Treatment of female DU includes strategies to ensure bladder drainage, increase bladder contraction, decrease urethral resistance, or a combination of the two [474]. The management goals for UAB are to improve symptoms and QoL, to reduce the risk of complications, and to identify situations where interventions may not be appropriate.

4.4.4.1 Conservative management

4.4.4.1.1 Behavioural interventions

Regular or timed voiding in women with impaired bladder sensations have been done to avoid bladder over-distention. Assisted voiding by abdominal straining with adequate relaxation of the PFM, double or triple voiding are potential strategies to improve bladder emptying. However, none of these manoeuvres has proven efficacy in an RCT. Furthermore, there is a possible association between voiding by excessive abdominal straining and the risk of POP [478]. A small retrospective study in women with neurogenic acontractile detrusor secondary to spina bifida showed that Valsalva voiding may increase the risk of rectal prolapse compared with CISC [479].

4.4.4.1.2 Pelvic floor muscle relaxation training with biofeedback

There are no RCTs on PFM relaxation training in adult women with UAB. Contrary to common beliefs, one study found significant relaxation of the PFMs after contraction [480] and another study found that PFM relaxation training over time increased the speed of relaxation after a single contraction [481]. There is some evidence from the paediatric literature, including one RCT that compared efficacy of PFM relaxation with biofeedback plus combined therapy (including hydration, scheduled voiding, toilet training and diet) vs. combined therapy alone in children with non-neuropathic UAB and voiding dysfunction. Mean number of voiding episodes was significantly increased in the relaxation training group compared with the group with only combined treatment. Post-void residual volume and voiding time decreased considerably, whereas maximum urine flow increased significantly in the relaxation group compared with the combined treatment group [482].

4.4.4.1.3 Clean intermittent self-catheterisation

Clean intermittent self-catheterisation is the most commonly used therapy to manage high PVR volume and urinary retention [117]. It reduces the risk of complications such as UTI, UUT deterioration, bladder stones and overflow UI, etc. It has not yet been established whether the incidence of UTI, other complications and user satisfaction, are affected by either sterile or clean intermittent catheterisation (IC), coated or uncoated catheters or by any other strategy [483]. The use of hydrophilic catheters may be associated with a lower rate of UTI, but further evidence is needed, as current data comes from neurogenic patients [484]. The average frequency of catheterisation is four to six times per day [485] and the catheter sizes most often used are 12–16 Fr. In aseptic IC, an optimum frequency of five times showed a reduction of UTI [485]. Frequency of catheterisation needs to be based on individual need and capability, to prevent chronic and repeated over-filling of the bladder [486]. Thorough counselling regarding techniques, frequency, equipment, and adverse effects of CISC should be given to all potential patients in line with good medical practice.

For people using CISC, a Cochrane review found no evidence that one type of catheter or regimen of catheterisation was better than another [487]. However, a recent narrative review suggests that, in certain populations, single-use catheters may reduce urethral trauma and UTI [488].

4.4.4.1.4 Indwelling catheter

Indwelling urinary catheter may be an option for some women who have failed all other treatments and are unable to perform CISC. Complications include UTI, stone formation, and urethral damage. Suprapubic catheterisation may be preferable over urethral catheterisation to minimise the risk of urethral trauma and pain [489].

4.4.4.1.5 Intravesical electrical stimulation

Intravesical electrical stimulation (IVES) can be used to improve bladder dysfunction by stimulating A-delta mechanoreceptor afferents but requires intact afferent circuits and healthy detrusor muscle. One retrospective study in sixteen patients (eleven females) found that two-thirds of patients with a weak detrusor after prolonged bladder over-distension regained balanced voiding after IVES due to detrusor reinforcement [490].

4.4.4.2 Pharmacological management

4.4.4.2.1 Parasympathomimetics

Theoretical approaches to UAB pharmacological treatment include direct stimulation of detrusor cell muscarinic receptors using parasympathomimetic agents such as carbachol or bethanechol or acetylcholinesterase inhibitors such as distigmine, pyridostigmine or neostigmine.

A SR on the use of parasympathomimetics in patients with UAB included ten RCTs (controls typically received placebo or no treatment). Three studies reported significant improvements relative to the control group, but six did not and one even reported significant worsening of symptoms. There was no evidence for differences between individual drugs, specific uses of such drugs, or in outcome measures [491]. The review concluded that the available studies do not support the use of parasympathomimetic for treating UAB, especially when frequent and/or serious adverse effects (gastrointestinal upset, blurred vision, bronchospasm, and bradycardia) are taken into account.

4.4.4.2.2 Alpha-adrenergic blockers

In order to improve bladder emptying, decreasing outlet resistance through sympathetic blockade at the bladder neck/urethra has been investigated. One prospective study with tamsulosin showed similar improvement in terms of uroflowmetry parameters (specifically in the percentage of patients who had a good therapeutic response) in women with BOO (39.4%) or DU (32.7%) [492]. Another longitudinal study including fourteen women with DU showed clinical and urodynamic improvements after tamsulosin [493]. A prospective single-blind RCT in female patients with DU compared the efficacy of alpha-blocker, cholinergic drugs, or combination therapy, with the latter exhibiting the best results [494].

4.4.4.2.3 Prostaglandins

Prostaglandins are prokinetic agents that promote smooth muscle contraction. Prostaglandins E2 and F2 have been used intravesically to treat urinary retention after surgery. A Cochrane review showed a significant association between intravesical prostaglandin and successful voiding among postoperative patients with urinary retention. However, the success rate was low (32%) with wide 95% CI, compared to placebo. The RCTs included in the pooled analysis were underpowered with methodological limitations and the event rate was very low, indicating a very low certainty of the evidence [495]. Intravesical prostaglandin treatment is rarely used, and further research is necessary before it can be taken up more widely.

4.4.4.3 Surgical management

4.4.4.3.1 Sacral nerve stimulation

Sacral nerve stimulation is often used for therapy of non-obstructive urinary retention. The mechanism of action has not been fully elucidated, but activation of afferent sensory pathways, modulation–activation of the central nervous system, and inhibition of inappropriate activation of the guarding reflex are some of the mechanisms proposed.

An RCT included 37 patients in the implantation arm and 31 in the standard medical therapy arm, showing a mean decrease in PVR volume and a mean increase in voided PVR volume compared to standard treatment [496]. A meta-analysis of seven studies also showed a mean difference in PVR volume reduction of 236 mL and a mean voided volume increase of 299 mL [497]. The response rate during the trial phase ranged from 33-90% (mean 54.2%) and the success rate of permanent implantation ranged from 55-100% (mean 73.9%), highlighting that patient selection is crucial [498].

The importance of careful patient selection has been emphasised with one study suggesting women with evidence of anatomical BOO, suspected loss of intrinsic detrusor contractility or neurogenic bladder dysfunction show lower response rates [499].

4.4.4.3.2 Onabotulinumtoxin A

OnabotulinumtoxinA intersphincteric injections in external striated urethral sphincter may improve voiding in patients with DU by reducing outlet resistance and reducing the guarding reflex. Some retrospective case studies have shown improvement in voiding symptoms, recovery of spontaneous voiding, and improvement in urodynamic parameters (reduction of voiding pressure and/or urethral closure pressures, reduced PVR volume) [500, 501]. The duration of symptomatic relief is short; typically, three months but the reported incidence of *de novo* SUI is low.

4.4.4.3.3 Transurethral incision of the bladder neck

Transurethral incision of the bladder neck has been described in a small series of women with refractory DU. In a retrospective case study, 40/82 (48.8%) women achieved satisfactory outcomes (spontaneous voiding with voiding efficiency ≥ 50%), but five (6.1%) patients developed SUI and two (2.4%) developed a vesico-vaginal fistula [502].

4.4.4.3.4 Myoplasty

One retrospective multicentre study reported the long-term results of latissimus dorsi detrusor myoplasty in patients with bladder acontractility, with 71% recovering complete spontaneous voiding, with a mean PVR volume of 25 mL [503]. No other groups have published their experience to reproduce these findings.

4.4.4.4 Summary of therapeutic evidence on detrusor underactivity

The level of evidence for most therapeutic interventions for DU is low. Only CISC remains as a gold standard to reduce the adverse consequences of a high PVR volume and incomplete voiding, in spite of the low level of evidence that supports this statement.

4.4.4.4.1 Summary of evidence and recommendations for underactive bladder

Summary of evidence	**LE**
Abdominal straining with relaxation of the PFM may improve bladder emptying but increases the risk of POP.	3
Pelvic floor muscle relaxation training may increase voiding episodes, decrease post-void residual volume and voiding time.	3
Clean intermittent self-catheterisation has proven efficacy in terms of effecting bladder emptying in patients who are unable to do so.	3
Indwelling transurethral catheterisation and suprapubic cystostomy are associated with a range of complications as well as an increased risk of UTI.	3
Intravesical electrical stimulation may be useful in some patients after prolonged bladder over-distension, but long-term efficacy remains unproven.	3
Parasympathomimetics do not improve clinical or urodynamic parameters of UAB and frequent and/or serious adverse effects may arise.	1b
Alpha-adrenergic blockers in women with UAB may be effective in improving voided volume and reducing PVR volume.	2b

Very low certainty evidence indicates that intravesical prostaglandins may promote successful voiding in patients with urinary retention after surgery.	1a
Sacral nerve stimulation improves voided volume and decreases PVR volume in women with DU.	1b
There is limited evidence for the effectiveness of onabotulinumtoxinA external urethral sphincter injections to improve voiding in women with UAB.	3
Transurethral bladder neck incision may improve voiding in women with DU, but complications (SUI, vesico-vaginal fistulae) may occur.	3
There is very limited evidence for the effectiveness of detrusor myoplasty for bladder acontractility.	3

Recommendations	Strength rating
Encourage double voiding in those women who are unable to completely empty their bladder.	Weak
Warn women with underactive bladder (UAB) who use abdominal straining to improve emptying about pelvic organ prolapse risk.	Weak
Use clean intermittent self-catheterisation (CISC) as a standard treatment in patients who are unable to empty their bladder.	Strong
Thoroughly instruct patients in the technique and risks of CISC.	Strong
Offer indwelling transurethral catheterisation and suprapubic cystostomy only when other modalities for urinary drainage have failed or are unsuitable.	Weak
Do not routinely recommend intravesical electrical stimulation in women with UAB.	Weak
Do not routinely recommend parasympathomimetics for treatment of women with UAB.	Strong
Offer alpha-adrenergic blockers before more-invasive techniques.	Weak
Offer intravesical prostaglandins to women with urinary retention after surgery only in the context of well-regulated clinical trials.	Weak
Offer onabotulinumtoxinA external sphincter injections before more-invasive techniques as long as patients are informed that the evidence to support this treatment is of low quality.	Weak
Offer sacral nerve stimulation to women with UAB refractory to conservative treatment.	Strong
Do not routinely offer detrusor myoplasty as a treatment for DU.	Weak

*4.4.5 **Follow-up***

Natural history and clinical evolution at long-term follow-up of women with DU is not well known. No longitudinal cohort studies are described in the literature. The interval between follow-up visits depends on patient characteristics, treatments given and the frequency of urinary complications.

4.5 Bladder outlet obstruction

*4.5.1 **Introduction***

Bladder outlet obstruction is defined by the ICS as *"obstruction during voiding, characterised by increased detrusor pressure and reduced urine flow rate"* [1]. Its precise diagnosis requires urodynamic evaluation including an assessment of pressure and flow.

Voiding dysfunction has previously been defined in Section 4.4. In women, voiding dysfunction can be caused by BOO or DU [1]. There are also non-obstructive causes and therefore voiding dysfunction, and BOO should not be used interchangeably. Another term that must be differentiated from BOO and voiding dysfunction is dysfunctional voiding, which is a specific and discrete form of voiding dysfunction characterised by an intermittent and/or fluctuating flow rate due to involuntary intermittent contractions of the peri-urethral striated muscle during voiding in neurologically normal individuals [113].

*4.5.2 **Epidemiology, aetiology, pathophysiology***

4.5.2.1 Epidemiology

Estimates of prevalence of BOO among women vary from 2.7-29% [504]. One large series of women undergoing urodynamic evaluation for LUTS found that ~20% are diagnosed with BOO. The wide variance is due to several factors, including differences in definitions and diagnostic criteria for female BOO, differences in study populations, and variation in study methods. The estimated prevalence rates of LUTS due to BOO in women are lower than those reported in men (18.7–18.9% vs. 24.3–24.7%) [505].

Prevalence of voiding LUTS is associated with age [54, 506, 507], parity [54, 508], prolapse [54, 508] and prior continence surgery [54, 508]. Bladder outlet obstruction has long been postulated to cause mainly voiding symptoms [509] but recent data from a series of 1,142 women referred for evaluation of LUTS suggest that storage symptoms may be predominant in women diagnosed with BOO, and excess daytime urinary frequency was the most common symptom reported by 69% [504].

4.5.2.2 Pathophysiology

Bladder outlet obstruction can be either anatomical (mechanical) or functional. In anatomical BOO, there is a physical or mechanical obstruction to the outflow of urine, whereas in functional BOO there is a non-anatomical, non-neurogenic obstruction of the outlet usually resulting from non-relaxation of the bladder neck, sphincter or PFM, or increased urethral sphincter tone or PFM contraction during voiding, as observed in patients with dysfunctional voiding.

Mechanisms for anatomical (mechanical) obstruction include external compression, fibrosis, stricture or injury to the urethra and kinking of the urethra due to POP. Progressive fibroblastic reaction around the urethra induced by mesh tapes or slings used in incontinence surgery may also cause anatomical (mechanical) obstruction [462]. In a retrospective review of 192 women diagnosed with BOO, 64% had mechanical obstruction [504].

Functional obstruction may be caused by contraction, or failure of relaxation, of the bladder neck and/or urethral sphincter complex or the PFMs during sustained detrusor contraction [509]. The exact causes of this lack of relaxation, or contraction, are often elusive but might be due to sympathetic hyperactivity or hypertrophy of the bladder neck smooth muscle for primary bladder neck obstruction [510], or may be mostly behavioural for dysfunctional voiding [511].

4.5.2.3 Aetiology

Conditions associated with anatomical BOO include POP, incontinence surgery, urethral stricture, urethral stenosis, urethral diverticulum, urethral caruncle, urethral malignancies and paraurethral masses.

Conditions associated with functional BOO include primary bladder neck obstruction, dysfunctional voiding, and idiopathic urinary retention (Fowler's syndrome).

In primary bladder neck obstruction, the bladder neck fails to open adequately during voiding, in the absence of an anatomical obstruction [512]. It is estimated that 4.6–16% of women presenting with voiding symptoms have primary bladder neck obstruction [510].

Dysfunctional voiding is due to involuntary intermittent contractions of the peri-urethral striated or levator muscles during voiding in neurologically normal women, and is thought to be caused by faulty learned toileting behaviour [462]. There is also some evidence of a link between dysfunctional voiding and a history of sexual abuse [513].

Idiopathic urinary retention, also known as Fowler's syndrome, is a primary disorder of the external urethral sphincter with hypertrophy of the muscle fibres, which fail to relax during micturition. It is associated with decreased detrusor contractility via enhancement of the guarding reflex. It is seen most often, but not exclusively, in young women with urinary retention and is characterised by increased urinary sphincter volume and activity/tone, which may be hormonally triggered [514].

Alpha-adrenergic agonists, such as pseudoephedrine commonly contained in decongestants, can lead to some form of functional obstruction due to their stimulatory effects, which may contract the bladder neck and lead to urinary retention [515].

Neurological conditions can also bring about functional BOO in women. These conditions are not considered in these guidelines and are covered elsewhere [9].

*4.5.3 **Classification***

4.5.3.1 Anatomic bladder outlet obstruction

Anatomical BOO involves a physical or mechanical obstruction of the outflow of urine not related to urethral or pelvic muscle tone.

4.5.3.2 Functional bladder outlet obstruction

Functional BOO involves a non-anatomical, non-neurogenic obstruction of the outflow of urine resulting from non-relaxation or increased tone in the bladder neck and/or urethral sphincter complex or the PFMs (Table

5). Neurological causes of functional BOO are not considered in these guidelines and are covered in the EAU Guidelines on Neuro-urology [9].

Table 5: Main causes of female bladder outlet obstruction

Functional BOO	Anatomical BOO
• Primary bladder neck obstruction • Dysfunctional voiding • Idiopathic urinary retention (Fowler's) syndrome	• Urethral stricture • Anti-incontinence surgery • Pelvic organ prolapse • Urethral diverticulum • Urethral caruncle • Urethral malignancies • Paraurethral masses

4.5.3.3 Recommendation for classification of bladder outlet obstruction

Recommendation	Strength rating
Use standardised classification of bladder outlet obstruction in women (anatomical or functional), and research populations should be fully characterised using such classification.	Strong

4.5.4 Diagnostic evaluation

Diagnosis of BOO in women, although dependent on formal pressure–flow studies, may be suggested by several clinical and other non-invasive assessments.

4.5.4.1 Clinical history

In terms of clinical history, a range of LUTS may be elicited and these may not be confined to voiding LUTS. Women may not present until they have the possible complications of BOO, such as recurrent UTI, chronic urinary retention or acute/chronic kidney disease [504]. The evidence regarding clinical utility of symptoms for the diagnosis of BOO is inconclusive and limited to small retrospective studies [516, 517]. Perhaps some of the difficulty in evaluating the diagnostic accuracy of urinary symptoms comes from the observation that a significant proportion of women presenting with obstruction also have concomitant storage symptoms, making urodynamic evaluation essential. In a large study of > 5,000 women with urinary symptoms including 163 with BOO, additional urodynamic diagnoses were noted in 54% [518].

4.5.4.2 Clinical examination

There are no studies evaluating the clinical utility of physical examination in women with suspected BOO; nevertheless, it is widely considered as a key part of the medical assessment. It allows for visual inspection of the urethra and vagina for possible causes of mechanical obstruction as well as an assessment of the pelvic floor, which may be the cause of functional obstruction.

4.5.4.3 Uroflowmetry and post-void residual volume

Reduced Q_{max} and incomplete bladder emptying can result from weakness in the contractile strength of the detrusor muscle, or increased outlet resistance due to functional or anatomical/mechanical BOO. The use of uroflowmetry to differentiate between anatomical and functional BOO was explored in a retrospective study of 157 women [511], which concluded that Q_{max} was significantly lower in patients with anatomical obstruction, but a large degree of overlap was noted. The largest evaluation of the diagnostic utility of urine flow studies and PVR volume estimation was a retrospective analysis of > 1,900 patients with symptoms of voiding dysfunction, of whom > 800 were diagnosed with BOO based on urodynamic assessment [519]. Functional BOO was > 6 times more common than anatomical/mechanical obstruction, which does not agree with most of the other epidemiological literature for female BOO. The authors found that although urine flow rate alone was not accurate enough to diagnose BOO, PVR of ≥ 200 mL could differentiate bladder neck dysfunction from the other causes of BOO, with a receiver-operator characteristics (ROC) area under the curve (AUC) of 0.69. Conversely, in a retrospective study involving 101 women primarily presenting with SUI, a good correlation between abnormal uroflowmetry and urodynamic obstruction (phi = 0.718) was found [520].

4.5.4.4 Ultrasound

The major utility of US scanning in women with BOO is to detect possible complications such as BWT/DWT upper tract dilatation/hydronephrosis. However, the diagnostic capabilities of US have been investigated in

a 2021 SR of 16 non-randomised studies and reported a moderate pooled sensitivity and high specificity for DWT, while 6 studies evaluating US-estimated bladder weight (UEBW) reported a high sensitivity and specificity [521]. A prospective case–control study of 27 patients with cystoscopically confirmed bladder neck obstruction [522] reported the diagnostic value of shear wave elastography (SWE) and acoustic radiation force impulse imaging (ARFI) for female BOO was compared and the authors concluded that ARFI was more accurate than SWE, but a combination of the techniques was superior to either one alone.

4.5.4.5 Magnetic resonance imaging

Magnetic resonance imaging in patients with pathological urethral stricture can determine the degree of peri-urethral fibrosis, although the prognostic and clinical significance of such a finding has not been established [523].

4.5.4.6 Electromyography

Electromyography (EMG) has been most extensively studied in the subgroup of women with BOO due to idiopathic urinary retention caused by a high-tone non-relaxing sphincter (Fowler's syndrome). Abnormal urethral EMG activity may be associated with non-relaxation of the striated sphincter, abnormally high urethral pressure, and, through an exaggerated guarding reflex, poor bladder sensation and reduced detrusor contractile strength [513, 524]. Complex repetitive discharges and decelerating bursts are specific urethral EMG abnormalities that have been described in patients with high-tone non-relaxing sphincter, although these abnormalities have also been noted in asymptomatic volunteers [525, 526]. A review of voiding dysfunction in women included 65 studies with only a small number addressing the diagnostic utility of PFM EMG [462]. The authors commented that increased EMG activity of the PFM can be seen during voiding or non-relaxation, and when this is coupled with pressure–flow information from urodynamics, it may be useful to differentiate between functional and anatomical obstruction. Further evidence for this comes from a retrospective study of 157 women with roughly equal numbers of women with functional and anatomical obstruction, which concluded that a low level of PFM EMG activity is characteristic of anatomical obstruction [511]. Additional neurophysiological tests, such as anal sphincter EMG, bulbocavernosus reflex, and pudendal sensory evoked potentials can assess the integrity of the somatic S2–4 nerve roots; however, their clinical utility in the context of non-neurogenic female BOO needs to be better defined [513].

4.5.4.7 Cystourethroscopy

Cystourethroscopy can be useful to visualise any anatomical/mechanical obstruction and provide information regarding its nature, location and calibre. Given that pelvic malignancy may cause anatomical BOO, cystourethroscopy is considered an essential part of the diagnostic pathway. Formal urethral calibration may be useful for women with BOO secondary to pathological urethral stricture and various different urethral calibre thresholds have been used, from 14-20 Fr [527].

4.5.4.8 Urodynamics and video-urodynamics

Pressure–flow studies are the mainstay of BOO diagnosis and the characteristic abnormalities are a combination of low flow and concomitant high detrusor pressure [512]. However, while the general definition of BOO is well established, with some data supporting its clinical validity in male patients [528], the urodynamic definition of female BOO remains controversial [509]. Several urodynamic criteria have been introduced but none has been established as a standard due to lack of clinical validation [509, 529]. The Blaivas-Groutz nomogram, which plots free Q_{max} and maximum detrusor pressure ($P_{det \cdot max}$) measured during urodynamic studies, is one of the most popular [530] but has been suggested to overestimate obstruction [531]. The addition of fluoroscopic imaging suggested by Nitti and colleagues introduces a video-urodynamic criterion for obstruction [76]. However, both methods lack data supporting their clinical validity, especially regarding their predictive value for therapeutic intervention outcomes [74].

In a large retrospective study of 1,914 patients, 810 of whom were diagnosed with BOO, several urodynamic cut-off values were determined by ROC curve analysis to optimise the diagnostic accuracy of video-urodynamic studies [519]:

- $P_{det}Q_{max} \geq 30$ cm H_2O for differentiating BOO from bladder dysfunction and normal studies (ROC AUC = 0.78);
- the Abrams-Griffiths number > 30 for differentiating anatomical from functional BOO (ROC AUC = 0.66);
- $P_{det}Q_{max} \geq 30$ cm H_2O for differentiating dysfunctional voiding from poor relaxation of the external sphincter (ROC AUC = 0.93).

More recently, Solomon and Greenwell devised a female BOO nomogram that parallels the ICS nomogram used for male BOO [532]. It allows the calculation of an alternative BOO female index (BOOIf), using a formula closely aligned to its male counterpart: $BOOIf = P_{det}Q_{max} - 2.2Q_{max}$.

It is interpreted with a different algorithm however:
- BOOIf < 0: < 10% probability of obstruction;
- 5 < BOOIf < 18: equivocal, ≥ 50% likelihood of obstruction;
- BOOIf > 18: 90% likelihood of obstruction.

The Solomon–Greenwell nomogram was the first to be tested for clinical validity. In a recent series of 21 unselected consecutive women treated for BOO, the authors observed significant improvement of all urodynamic parameters (Q_{max}, $P_{det}Q_{max}$ and BOOIf) in female patients who became asymptomatic postoperatively [533].

An alternative urodynamic parameter of area under the detrusor pressure curve during voiding (corrected for voided volume) has been proposed following a prospective study of 103 women [534]. The authors concluded that this variable appears to be the most discriminating urodynamic parameter for the diagnosis of female BOO. This suggested diagnostic method has not been independently validated.

Voiding cystourethrography (VCUG) alone or in conjunction with concomitant pressure–flow studies may be useful in delineating the site of obstruction. Characteristic features include:
- radiographic evidence of obstruction between the bladder neck and distal urethra in the presence of sustained detrusor contraction [76];
- lack of funnelling appearance of the bladder neck/tight bladder neck in primary bladder neck obstruction;
- proximal dilatation of the urethra with distal narrowing in women with urethral stricture disease or pelvic-floor hypertonicity.

IIt is not uncommon for women with voiding dysfunction, specifically functional BOO, to be unable to provide a flow during (video)urodynamic testing. Failure to relax the PFM can enhance the guarding reflex, limiting detrusor contractility.

4.5.4.9 Summary of evidence and recommendations for diagnosis of bladder outlet obstruction

Summary of evidence	**LE**
Evaluation of LUTS by history and examination alone is insufficient to accurately diagnose female BOO.	3
Urine flow studies cannot accurately diagnose BOO in women.	3
Ultrasound scanning is unable to accurately diagnose BOO in women.	2b
Electromyography alone is unable to accurately diagnose BOO in women, although it may be of use in combination with pressure–flow studies and in differentiation of anatomical vs. functional BOO.	3
Cystourethroscopy can be useful to visualise any anatomical/mechanical obstruction and provide information regarding its nature, location, and calibre.	4
Urodynamics (often combined with video-fluoroscopy) is the standard test for evaluating female BOO.	3

Recommendations	**Strength rating**
Take a full clinical history and perform a thorough clinical examination in women with suspected bladder outlet obstruction (BOO).	Strong
Do not rely on measurements from urine flow studies alone to diagnose female BOO.	Strong
Perform cysto-urethroscopy in women with suspected anatomical BOO.	Strong
Perform urodynamic evaluation in women with suspected BOO.	Strong

*4.5.5 **Disease management***

Therapeutic interventions for BOO aim to decrease outlet resistance in order to increase urinary flow, improve bladder emptying and thus reduce voiding and storage LUTS [74, 509, 529]. Treatment choice is commonly dictated by the underlying cause of the obstruction.

4.5.5.1 Conservative management

4.5.5.1.1 Behavioural modification

Behavioural modification interventions are often tailored to individual patients' needs, symptoms and circumstances and can include elements such as education regarding normal voiding function, self-monitoring of symptoms, changes in lifestyle factors that may affect symptoms, avoidance of constipation, and alteration of voiding technique. Ultimately, techniques aim to improve the coordination between the detrusor and sphincter, resulting in their synergistic action [74, 509, 529].

These individual components of self-management have not been evaluated separately and most recommendations are derived from consensus methodology. They may help reduce symptoms resulting from BOO but no quantification of their effect is possible.

4.5.5.1.2 Pelvic floor muscle training +/- biofeedback

In the context of BOO, physiotherapy aims to teach patients to relax their PFMs and striated urethral sphincter during voiding. Pelvic floor muscle contraction, particularly in women with pelvic floor dysfunction, has been shown to significantly reduce vaginal resting pressure and surface EMG activity [480].

As mentioned in the section discussing UAB (Section 4.4.4.1.2), most of the evidence supporting PFMT in dysfunctional voiding is from paediatric studies.

4.5.5.1.3 Electrical stimulation

Application of electrodes that allow for controlled contraction and relaxation of the PFMs may theoretically facilitate the relaxation of the external sphincter and pelvic floor but no critical evaluation of this intervention in women with BOO has been published.

4.5.5.1.4 Use of vaginal pessary

Intravaginal devices such as pessaries aim to relieve voiding symptoms and improve bladder emptying by physical correction of the obstruction caused by a POP. In a prospective study of eighteen women with grade three or four cystocoeles and diagnosed with BOO by urodynamics (defined as $P_{det}Q_{max}$ > 25 cm H_2O, Q_{max} < 15 mL/s), normal voiding was noted in seventeen (94%) immediately after placement of a vaginal pessary. No other outcomes were available in this series [535]. No long-term data are available on the use of vaginal pessary for BOO.

4.5.5.1.5 Urinary containment

The use of containment devices in BOO is to achieve social continence in patients with urinary retention and associated overflow UI and is often only a temporary measure. There are no published studies on the outcomes or adverse events associated with the use of urinary containment devices for the management of female BOO, though there are many involving women with UI who may have BOO as an underlying cause.

4.5.5.1.6 Urinary catheterisation

Significant urinary retention from BOO may be addressed by actively bypassing the obstruction and draining the residual urine. Catheterisation may be used as a treatment itself or as an adjunct to an initial treatment of urethral dilatation or urethrotomy or bladder neck incision. There are two ways of using a catheter: CISC or indwelling catheterisation [117].

After UI surgery, BOO may be managed by short-term catheterisation in most patients who have transient postoperative voiding difficulty. For a few women who develop chronic urinary retention, CISC or indwelling catheterisation may be offered [462].

A small RCT investigated the effectiveness of CISC to prevent recurrence after internal optical urethrotomy for urethral stricture disease. In the treatment group, CISC was done twice a day for one week, and once a day for four weeks, then once weekly for seven weeks post-urethrotomy. Freedom from stricture recurrence, determined by urethrography and uroflowmetry performed twelve weeks postoperatively, was higher in the catheterisation group compared to the group with no catheterisation (78.5% vs. 55.4%) [536]. This finding mirrors the Cochrane review on self-dilatation for urethral stricture among men that showed less recurrence with the performance of self-dilatation [537].

In a series of 20 patients with voiding dysfunction after TVT who were put on a CISC programme, overall cure rate was 59%, with cure defined as consistent residual volume < 100 mL. Half of these patients were voiding normally within twelve weeks [538].

See Section 4.4.4.1.3 for further evidence related to CISC.

4.5.5.1.7 Intraurethral inserts

An intraurethral insert is a short silicone catheter containing an internal valve and pump mechanism positioned in the female urethra. The valve-pump mechanism is operated by an external control unit, which activates to open the valve and the pump to draw urine from the bladder and allow voiding. At the end of urination, the pump ceases and the valve closes to regain continence. The insert is routinely replaced once a month.

One study reported the use of this device in 92 women with voiding dysfunction of various aetiologies including multiple sclerosis, prior pelvic surgery, pelvic radiation, diabetes mellitus, spinal stenosis and injury. The device was removed within seven days of insertion in 60% of the cases due to discomfort, peri-catheter leakage or technical difficulty. An additional 20% of patients had late discontinuation. All those who continued to use the device were satisfied, with PVR volumes remaining < 100 mL. Adverse events included migration into the bladder in six cases and symptomatic UTI in four cases [539, 540]. Extended, long-term data on the use of urethral inserts are not available.

4.5.5.1.8 Extracorporeal magnetic stimulation

Extracorporeal magnetic stimulation involves the patient sitting on a device that induces consistent PFM contraction and relaxation at a set frequency and interval by repeated magnetic stimulation of motor nerve fibres. It is postulated that patients therefore learn to spontaneously contract or relax the PFM, which may enhance their ability to relax their pelvic floor while voiding [541].

In a small (n = 60) prospective non-randomised trial, alfuzosin was compared to EMS and to the combination of alfuzosin + EMS in women with functional BOO. They observed significant increase of Q_{max} and significant decrease of International Prostate Symptom Score (IPSS) in all groups and significantly greater improvement in the QoL question of the IPSS in the combination therapy group [541].

4.5.5.1.9 Summary of evidence and recommendations for conservative treatment of bladder outlet obstruction

Summary of evidence	**LE**
Pelvic floor muscle relaxation training with biofeedback may result in relaxation of the pelvic muscles and external urethra in women with dysfunctional voiding.	3
There is no available evidence in the published literature on the clinical effect of ES for management of female BOO.	NA
In women with large (grade three or four) cystocoeles causing BOO, placement of a vaginal pessary may improve voiding efficiency.	3
Regular CISC after urethrotomy is better than no catheterisation to prevent recurrence of urethral strictures.	1b
A CISC programme in women with voiding dysfunction after TVT has a cure rate of 59%.	3
Women who use an intraurethral device have lower PVR volume, but most require its removal due to complications.	3
Extracorporeal magnetic stimulation combined with alfuzosin may be more effective than either of these therapies alone in women with functional BOO.	2a

Recommendations	**Strength rating**
Offer pelvic floor muscle training (PFMT) aimed at pelvic floor muscle relaxation to women with functional bladder outlet obstruction (BOO).	Weak
Prioritise research that investigates and advances understanding of the mechanisms and impact of PFMT on the coordinated relaxation of the pelvic floor during voiding.	Strong
Offer the use of a vaginal pessary to women with grade three or four cystocoeles and BOO who are not eligible/inclined towards other treatment options.	Weak
Offer urinary containment devices to women with BOO to address urinary leakage as a result of BOO, but not as a treatment to correct the condition.	Weak
Offer clean intermittent self-dilatation to women with urethral strictures or post-urinary incontinence surgery for BOO.	Weak
Do not offer an intraurethral device to women with BOO.	Strong

*4.5.6 **Pharmacological management***

4.5.6.1 Alpha-adrenergic blockers

Alpha-adrenergic blockers are postulated to relieve LUTS caused by BOO in women via smooth muscle relaxation in the bladder neck, thus decreasing bladder outlet resistance [542].

Systematic reviews on the use of alpha-blockers in women generally involve studies with a population that includes women complaining of LUTS and voiding dysfunction. Confirmation of BOO is often not required in the trials included [543, 544]. These reviews showed significant improvements in symptoms and urodynamic parameters associated with their use [543-545]. A meta-analysis of fourteen RCTs comparing alpha-blockers and placebo in women with LUTS showed significant symptom relief after alpha-blocker treatment relative to placebo, but no significant difference in Q_{max}, PVR volume and adverse event rates [543]. This is in contrast to prospective non-comparative trials that consistently showed improvements in voiding and storage symptoms, bother scores, and urodynamic parameters (Q_{max}, PVR, $P_{det}Q_{max}$, MUCP after alpha-blocker use compared to baseline) [492, 493, 546-548].

A SR performed by the Panel of studies on alpha-blockers used specifically for women with BOO included one placebo-controlled RCT, one RCT comparing two types of alpha-blockers, and six prospective non-comparative studies [150]. In the only placebo-controlled RCT reporting subgroup analyses in women with urodynamically proven BOO (based on the Blaivas-Groutz nomogram) no significant difference was observed in the changes of IPSS, IPSS sub scores, Q_{max}, PVR volume and bladder diary after eight weeks of alfuzosin (n = 58) vs. placebo (n = 59). Of note, no EMG and/or voiding cysto-urethrography was used to distinguish between dysfunctional voiding and primary bladder neck obstruction [549].

Information on the comparative effectiveness of the different types of alpha-blockers was limited to one RCT. A small trial of 37 women with IPSS > 8, Q_{max} < 12 mL/s and PVR volume > 50 mL, compared tamsulosin and prazosin over a three-month treatment period. More patients treated with tamsulosin were completely satisfied with their treatment (16/20 vs. 9/20). Both treatment groups showed significant improvement in symptom scores from baseline but no further statistical comparison between the groups was done. However, a larger decrease in AUA symptom score was seen in the tamsulosin group compared with the prazosin group. More adverse events were reported with prazosin (thirteen vs. one case) [550].

4.5.6.2 Striated muscle relaxants

Baclofen is a gamma-aminobutyric acid (GABA) agonist that exerts its effect on the GABAergic interneurons in the sacral inter-mediolateral cell column responsible for the relaxation of the striated urinary sphincter during voiding.

A randomised placebo-controlled crossover trial investigated the efficacy and safety of a four-week course of oral baclofen 10 mg three times/day in 60 women diagnosed with BOO, based on increased EMG activity with sustained detrusor contraction during voiding. It showed a lower number of voids, significant improvements in Q_{max} and $P_{det}Q_{max}$ with baclofen compared with placebo. PVR volume, maximum cystometric capacity and MUCP were not significantly different between the groups. Adverse event rates were also similar, with the most common being somnolence, dizziness, and nausea. An important limitation of this study was the lack of patient-reported outcomes to assess symptoms and QoL [551].

4.5.6.3 Oestrogens

The relative reduction in urethral wall compliance seen in atrophic urethritis due to oestrogen deprivation may be responsible for urethral obstruction in postmenopausal women. Oestrogen therapy is thus theoretically expected to improve the condition. There are no published studies on the use of oestrogens specifically for the management of female BOO.

4.5.6.4 Sildenafil

Sildenafil, by inhibiting phosphodiesterase five, increases the levels of nitric oxide in the female urethral sphincter, thereby promoting urethral relaxation.

A placebo-controlled, randomised crossover trial that included twenty women with partial or complete retention or obstructive voiding, with high MUCP and elevated US-estimated sphincter volume (> 1.6 cm) showed that while there was significant improvement in symptom scores and urodynamic parameters from baseline with sildenafil treatment, this difference was not significant when compared with placebo [552].

4.5.6.5 *Thyrotropin-releasing hormone*

Intravenous thyrotropin-releasing hormone (TRH) has been postulated as a neurotransmitter that induces urethral relaxation [553]. The exact mechanism is unclear.

In a small RCT of sixteen women with voiding difficulty, eight (three with BOO) were randomised to receive 200 µg intravenous bolus of TRH, and eight (three with BOO) received saline. No difference in the decline in functional profile lengths and maximum urethral closure pressures were noted between treatment groups, despite a significant decline noted from baseline in the treatment group. No subgroup analysis of women with BOO was reported [553].

4.5.6.6 *Summary of evidence and recommendations for pharmacological management*

Summary of evidence	**LE**
Alpha-adrenergic blockers may be associated with improvement in symptom scores from baseline, but not urodynamic parameters compared with placebo.	1a
Tamsulosin is associated with greater improvement in symptom score compared with prazosin.	1b
Oral baclofen is better than placebo in improving Q_{max} and $P_{det}Q_{max}$, but not other urodynamic parameters. Its effects on symptoms are not well reported.	1b
Current evidence does not show that sildenafil is superior to placebo in improving symptoms or urodynamic parameters of female patients with BOO.	1b
Trials including women with voiding problems of mixed aetiologies showed no difference in urodynamic outcomes between intravenous TRH and placebo.	1b

Recommendations	**Strength rating**
Offer uroselective alpha-blockers, as an off-label option, to women with functional bladder outlet obstruction (BOO) following discussion of the potential benefits and adverse events.	Weak
Offer oral baclofen to women with BOO, particularly those with increased electromyography activity and sustained detrusor contraction during voiding.	Weak
Only offer sildenafil to women with BOO as part of a well-regulated clinical trial.	Strong
Do not offer thyrotropin-releasing hormone to women with BOO.	Strong

4.5.7 ***Surgical management***

4.5.7.1 *Intra-sphincteric botulinum toxin injection*

Botulinum toxin inhibits the presynaptic release of acetylcholine, which reduces urethral sphincter tone. It is also believed to decrease the release of noradrenaline in the urethra to counteract external urethral sphincter overactivity [554].

Evidence on the use of botulinum toxin for female BOO is limited to small case series. Most studies included mixed populations without subgroup analyses, or the diagnosis of voiding dysfunction could not be ascertained as solely resulting from BOO. No comparative trial exclusively involving female BOO patients using botulinum toxin has been identified in the literature.

A SR including several reports of small case series using variable doses of onabotulinumtoxinA injected periurethrally in women with dysfunctional voiding showed improvements in symptoms, and reductions in residual volume and voiding detrusor pressure. Larger series in adults (both sexes) showed success rates of 86–100% [554].

A double-blind, placebo-controlled RCT (n = 73) resulted in significantly lower IPSS score and larger voided volume after 100 U onabotulinumtoxinA compared with saline in 31 men and women with dysfunctional voiding. Dysfunctional voiding was defined by a spinning top appearance on real-time fluoroscopy, poorly relaxed urethral sphincter on EMG, and a normal-to-high voiding pressure with a low and/or intermittent urinary flow rate, a PVR volume > 300 mL, and a low voiding efficiency. Other urodynamic parameters were comparable between the groups [555]. A subgroup analysis on the female population of this study was not available.

Two small case series in women with BOO reported the effects of intrasphincter 100 U onabotulinumtoxinA. Both showed improvement in symptom and bother scores and significant reduction in PVR volume [513, 556]. One study reported increased Q_{max} and improved static urethral pressure profile (UPP) [513]. The average symptom-free duration was 16.8 weeks in another study [556]. Adverse events included UTI and temporary need for CISC. No SUI was reported.

4.5.7.2 Sacral nerve stimulation

Sacral nerve stimulation is postulated to decrease urethral tone and to work by blockade of the inhibitory urethral afferent impulses, which cause inhibition of normal bladder contraction.

No comparative trial has been identified in the literature on the use of neuromodulation for female BOO.

Most publications on neuromodulation for voiding dysfunction are retrospective reviews of cases, involving a mix of patient populations who underwent the procedure for different indications. In studies that indicated a subgroup of patients with urinary retention, there was either no urodynamic confirmation of the nature of the retention or separate outcomes were not reported for participants with retention.

A review of 60 women who underwent SNS for urinary retention associated with outlet obstruction (defined as UPP > 100 cm H_2O, increased urethral sphincter volume > 1.8 mL, and abnormal EMG with repetitive discharges and decelerating bursts) showed an overall spontaneous voiding rate of 72% over a mean follow-up of four years. Of those who continued to require CISC up to twice daily postoperatively, the frequency was less than prior to surgery (degree not specified). There were 99 adverse events and 63 surgical revisions. In this series, half of the patients underwent a one-stage SNS procedure and the other half a two-stage procedure. The proportion of patients who required CISC-assisted voiding was higher in the two-stage group (27% vs. 17%). More serious adverse events (defined as events requiring admission or surgical revision to resolve issues such as loss of response, lead migration and surgical revisions) were associated with the one-stage procedure [557].

4.5.7.3 Pelvic organ prolapse surgery

Pelvic organ prolapse surgery may relieve BOO by correcting the urethral kinking caused by the prolapse or by relieving the urethral compression brought about by the prolapsing organ [74, 509, 529].

Bladder outlet obstruction due to POP may be addressed by corrective surgery. Based on reviews, the majority of patients who had BOO caused by POP who had repair of their cystocoele demonstrated improvement of their voiding difficulties [462, 558].

A multicentre prospective study involving 277 women with at least grade two symptomatic POP who underwent surgery demonstrated a significant reduction in voiding symptoms and PVR volume one year postoperatively [559].

A retrospective study of 50 women who underwent laparoscopic sacrocolpopexy for POP showed a significant increase in mean postoperative Q_{max} and decrease in $P_{det}Q_{max}$ and PVR in those aged ≥ 65 years. The OAB symptom score improved but there was no significant difference in the ICIQ-SF score postoperatively [560].

4.5.7.4 Urethral dilatation

Urethral dilation involves the passage of sequentially greater diameter dilators into the urethra, causing the obstructing fibrotic tissue to break open, thereby widening the lumen. It is considered the primary procedure of choice for women suspected of urethral stricture disease [527]. Dilation of up to 30–40 Fr has been done. There is no standard dilatation technique; dilatation of up to 43 Fr has been described, although other authors suggest dilating to 30 or 35 Fr.

A systematic review of female urethral stricture management included three trials involving urethral dilatation. Pooled analysis of data from 93 women showed a mean success rate of 49% after urethral dilation to 41 Fr with a mean follow-up of 46 months. Mean time to failure was 12 months. In treatment-naïve patients, success rate (as defined by trialists) was 58%, compared with 27.2% in patients who had undergone previous dilatation [561].

An RCT of 50 women with OAB syndrome and associated urodynamically confirmed BOO (defined as a Q_{max} < 15 mL/s with a voided volume of ≥ 100 mL and/or PVR volume > 200 mL, not due to urethral stricture) compared the effect of cystoscopy and bladder distension with urethral dilatation (n = 22) and cystoscopy only (n = 28) after six weeks' follow-up. Significantly more patients who had cystoscopy only had persistent urgency at six weeks and six months postoperatively. Urodynamic parameters did not significantly change

pre- and postoperatively in both groups. The greater improvement in QoL scores based on the King's Health Questionnaire domain scores seen in the non-urethral dilatation group in this trial should be interpreted cautiously because of the higher baseline scores. There were no significant changes in Q_{max}, PVR volume, voided volume or $P_{det}Q_{max}$ in any of the two groups at six weeks' questioning the role of any of these two options for therapeutic management of BOO. Also, six patients (12%) developed postoperative SUI [562].

A prospective trial of 86 women with primary urethral stricture compared on-demand vs. intermittent urethral dilatation to 24 Fr every two months. It showed an overall increase in Q_{max} and decrease in PVR volume post-dilatation. Significantly greater improvements were seen in the intermittent urethral dilatation group [563].

Worsening or new-onset SUI is a concern with urethral dilatation, but it is less of a concern than after urethrotomy or surgical reconstruction. Patients have also reported frequency and urgency post-dilatation [564].

4.5.7.5 Urethrotomy

Urethrotomy involves incision of the urethra endoscopically or using a urethrotome. It addresses the urethral narrowing by cutting open the scar tissue which is causing the obstruction [74, 509, 529, 564].

A prospective study of ten women with urethral strictures investigated the effect of Otis urethrotomy to 40 Fr followed by six weekly dilatations. There was significant improvement in IPSS, QoL, voided volume, Q_{max} and PVR volume at six months. Only the improvements in PVR volume and QoL were maintained on long-term follow-up (mean 82 months) [565].

4.5.7.6 Bladder neck incision/resection

Transurethral bladder neck incision decreases resistance at the bladder neck by cutting open the hypertrophic bladder neck smooth muscle in patients with primary bladder neck obstruction. Transurethral incision of the bladder neck may be performed with a unilateral incision at the twelve o'clock position or with bilateral incisions at the five and seven o'clock, two and ten o'clock or three and nine o'clock positions, or four incisions at the three, six, nine and twelve o'clock positions. This may be done using a resectoscope with a Collin's knife, cold knife, or using laser energy. Some authors report additional resection of the bladder neck between the five and seven o'clock positions.

A review of non-comparative studies on bladder neck incision for the treatment of bladder neck obstruction in women reports success rates of 76–100% [512].

Bladder neck incision was compared with V-Y-reconstruction using Nesbit's technique in a retrospective study of seventeen women with BOO, diagnosed by various uroradiological, endoscopic and urodynamic investigations. The results showed similar symptomatic improvement rates and postoperative PVR volume between the two groups. V-Y plasty had a longer operating and catheter time, lower uroradiological improvement rate, higher transfusion rate, and higher adverse event rate [566].

Several prospective case series consistently reported significant improvements in IPSS, QoL, Q_{max}, $P_{det}Q_{max}$ and PVR volume after treatment compared to baseline, regardless of the site of the incision, type of energy used or the length of follow-up [567-570].

The largest case series with 84 patients diagnosed with primary bladder neck obstruction (based on lack of funnel shape of the bladder neck during voiding-on-voiding cysto-urethrography, P_{det} > 20 cm H_2O and Q_{max} < 12 mL/s) showed success in 84.5% of patients with improvement in IPSS, QoL, Q_{max} and $P_{det}Q_{max}$ after mean follow-up of 27.4 months (6–78 months). Complications included vesico-vaginal fistula (VVF) (3.6%), SUI (4.7%) and urethral stricture (3.6%) [567].

No comparisons have been made between the different incision techniques (location, length, and depth of incision, implement used – cold knife vs. hot knife vs. laser, with or without resection). However, in a case series of 84 patients, complications of VVF and SUI were noted in the cohort of patients who had their incisions at five and seven o'clock positions, and not in those who had their incisions at two and ten o'clock [567].

Adverse events include SUI, requirement for reoperation, and recurrence. Postoperative SUI was reported in 3– 33% [512].

4.5.7.7 Urethroplasty/urethral reconstruction

Surgical reconstruction of the female urethra has been used in the management of extensive urethral stricture. Several urethroplasty techniques include the use of vaginal or labial flaps, as well as vaginal and buccal grafts after cutting open the fibrotic tissue causing the urethral obstruction [571]. The use of bladder flaps has also been reported [572], and laboratory-engineered tissue grafts have also been used [572].

The surgical approaches have been described based on the position relative to the urethra; dorsal, ventral, or circumferential. The dorsal approach is believed to provide better mechanical support and a more vascularised bed for a graft or flap. However, there is greater risk of damage to the sphincter and clitoral bodies with this approach. The ventral approach is more familiar to most surgeons and requires less urethral mobilisation. However, it is reported as being more prone to urethrovaginal fistulae, although it is not clear to what extent [527].

Reviews of studies reporting outcomes of urethroplasty state success rates of 57–100% [573]. Pooled analysis from six studies using vaginal or labial flaps showed a mean success rate of 91% with a mean follow-up of 32 months. Vaginal or labial graft urethroplasty was reported to have an 80% success rate with a mean follow-up of 22 months.

Oral mucosal grafts, reported in seven studies, had a mean success of 94% after a mean follow-up of fifteen months [527]. A later review of studies on dorsal buccal mucosal graft reported success rates of 62–100%, with a pooled success rate of 86% [574]. A long-term study with a mean follow-up of 32 months showed a stricture recurrence rate of 23.1% [573].

4.5.7.8 Urethrolysis

Bladder outlet obstruction in women occurring as a complication of surgery for SUI may be managed surgically by urethrolysis, to regain urethral mobility. Urethrolysis may involve removal of peri-urethral anti-incontinence sutures, scar tissue and fibrosis.

Case series showed success rates measured as improved voiding and lower residual volumes, improvement, or resolution of symptoms and QoL, and improvement of urodynamic parameters after treatment [575-577]. *De novo* SUI was reported in 39% in one study [577]. Another study reported an association of persistent postoperative bladder symptoms with greater delay to performing urethrolysis [578].

4.5.7.9 Removal/excision/section/loosening of mid-urethral sling

In women who develop BOO after placement of a mid-urethral sling, surgical management may include tape loosening, incision or division, and excision and/or removal of the tape [462].

Several small retrospective reviews of cases using different techniques of sling revision (incision, partial excision, or excision) showed good success rates in terms of symptom reduction, resumption of voiding with significant reduction in PVR volume and improvement of urodynamic parameters. Stress urinary incontinence recurs in a small proportion of patients and often to a lesser degree than prior to the sling procedure. Studies have shown long-term efficacy, including preservation of continence.

In a series of 63 women who presented with voiding dysfunction and persistent PVR volume > 100 mL after tape surgery for UI, different techniques were compared. Comparisons involved sling revision: sling division (n = 46) vs. partial sling excision (n = 13) vs. sling revision (division or excision) with an additional anti-SUI procedure (n = 4). The authors reported an overall success rate of 87% (PVR volume < 150 mL). No significant difference in success rates was demonstrated among the different revision techniques. There was a greater need for surgery for recurrent SUI in the partial sling excision group without an anti-SUI procedure (23% vs. 2.2 and 0) [579].

One study showed that patients who underwent surgical release > 180 days after initial anti-UI surgery had significantly less recurrent SUI compared with patients who underwent the release sooner (15% vs. 46%) [580].

4.5.7.10 Summary of evidence and recommendations for surgical management of bladder outlet obstruction

Summary of evidence	**LE**
Intrasphincteric injection of botulinum toxin results in the improvement of symptoms and urodynamic parameters.	2
Sacral nerve stimulation results in spontaneous voiding and a reduction in CISC rate in the majority of female BOO patients in idiopathic urinary retention.	3

More serious adverse events and surgical revisions were associated with the one-stage neuromodulator implantation procedure.	3
Repair of POP improved PVR and voiding symptoms.	3
Urethral dilatation in women with BOO results in significant improvement in OAB symptoms, but improvements in urodynamic parameters of voiding are inconsistent.	1b
Programmed intermittent urethral dilatation results in better outcomes compared with on-demand dilatation.	3
Effects of urethral dilation are poorly sustained, requiring repeat intervention in the long term.	3
Internal urethrotomy followed by regular dilatations resulted in significant improvement in symptoms and urodynamic parameters in women with BOO.	3
Bladder neck incision in females with BOO results in improvements in symptoms and urodynamic parameters.	3
Complications of bladder neck incision are not common, but include VVF, SUI, and urethral stricture.	3
Urethroplasty using grafts or flaps in women with BOO due to urethral stricture have good success rates with significant improvements of symptoms, QoL scores and urodynamic parameters compared to baseline.	3
Urethroplasty results in better QoL and Q_{max} compared to urethral dilatation.	2
Long-term results showed significant stricture recurrence rate after urethroplasty.	3
Urethrolysis performed on women with voiding problems after anti-UI surgery resulted in improvements in symptoms, QoL and urodynamic parameters post-operatively.	3
Delayed urethrolysis was associated with persistent post-operative bladder symptoms.	3
Sling revision in women who presented with urinary retention or voiding problems and significant PVRs after sling surgery for UI resulted in improvements in symptoms and urodynamic parameters, resumption of voiding and reductions in PVRs.	3
Sling revision is associated with the risk of recurrent SUI.	3

Recommendations	**Strength rating**
Offer intra-sphincteric injection of botulinum toxin to women with functional bladder outlet obstruction (BOO).	Weak
Offer sacral neuromodulation to women with functional BOO.	Weak
Advise women with voiding symptoms associated with pelvic organ prolapse that symptoms may improve after surgery.	Weak
Offer urethral dilatation to women with urethral stenosis causing BOO but advise on the likely need for repeated intervention.	Weak
Offer internal urethrotomy with postoperative urethral self-dilatation to women with BOO due to urethral stricture disease but advise on its limited long-term improvement and the risk of postoperative urinary incontinence (UI).	Weak
Do not offer urethral dilatation or urethrotomy as a treatment for BOO to women who have previously undergone mid-urethral synthetic tape insertion due to the theoretical risk of causing urethral mesh extrusion.	Weak
Inform women of limited long-term improvement (only in terms of post-void residual volume and quality of life) after internal urethrotomy.	Weak
Offer bladder neck incision to women with BOO secondary to primary bladder neck obstruction.	Weak
Advise women who undergo bladder neck incision on the small risk of developing stress urinary incontinence (SUI), vesico-vaginal fistula or urethral stricture postoperatively.	Strong
Offer urethroplasty to women with BOO due to recurrent urethral stricture after failed primary treatment.	Weak
Caution women on the possible recurrence of strictures on long-term follow-up after urethroplasty.	Weak
Offer urethrolysis to women who have voiding difficulties after anti-UI surgery.	Weak

Offer sling revision (release, incision, partial excision, or excision) to women who develop urinary retention or significant voiding difficulty after tape surgery for UI.	Strong
Caution women about the risk for recurrent SUI and the need for a repeat/concurrent anti-UI surgery after sling revision.	Strong

*4.5.8 **Follow-up***

Women with BOO should be followed up and monitored regularly due to the risk of further deterioration of voiding or renal function in case of persistence and progression of the obstruction. For those who received treatment, monitoring must be done for recurrence of BOO. In particular, women who undergo urethral dilation, urethrotomy or urethroplasty for urethral stricture need to be monitored for stricture recurrence.

4.6 Nocturia

Nocturia was defined by the ICS in 2002 as "*the complaint that the individual has to wake at night one or more times to void*" and quantified in an updated document in 2019 as "*the number of times an individual passes urine during their main sleep period, from the time they have fallen asleep up to the intention to rise from that period*" [581]. The EAU Guidelines Panel on Urinary Incontinence conducted a SR on nocturia in women [582]. The search covered evidence up to 2017 and this review was updated with a scoping search in 2020.

*4.6.1 **Epidemiology, aetiology, pathophysiology***

The prevalence of nocturia varies according to age with 4–18% of women aged 20–40 years experiencing ≥ 2 episodes per night, compared to 28–62% of women aged ≥ 70 years [583]. In a study of 1,000 community-dwelling older adults, female nocturia was associated with older age, African American race, history of UI, lower limb oedema and hypertension [584]. A report on > 5,000 adults aged 30–79 years identified around 28% with nocturia and found additional correlates with increased cardiac disease, type 2 diabetes, and diuretic use [585]. A SR and meta-analysis with moderate certainty evidence based on the GRADE approach, demonstrated that the higher incidence of nocturia among hypertensive patients was more strongly associated (1.2 to 1.3-fold) among Black and Asian women, unrelated to their age or BMI status [586]. Another SR with moderate certainty of evidence based on the GRADE approach showed that nocturia was associated with a 1.2-fold increased risk of falls and possibly an approximately 1.3-fold increased risk of fractures [587]. Another SR and meta-analysis concluded that nocturia is probably associated with an ~1.3-fold increased risk of death [587].

The aetiology of nocturia is multifactorial and can include both urological and non-urological causes. Urological conditions which may exhibit nocturia as a significant symptom include OAB syndrome, BOO, DU, and dysfunctional voiding. Non-urological causes include 24-hour polyuria (which includes nocturnal polyuria), congestive heart failure, sleep apnoea, restless leg syndrome, peripheral vascular disease, sleep disorders, night-time food ingestion, dependent oedema, and excessive fluid intake [588]. Given the varied aetiology of this symptom, there are a range of possible pathophysiological mechanisms, including: (1) 24-hour polyuria (e.g., diabetes mellitus, primary polydipsia, and diabetes insipidus); (2) nocturnal polyuria (e.g., behavioural, peripheral oedema, obstructive sleep apnoea, glycosuria, hormonal abnormalities and cardiac dysfunction); (3) diminished bladder capacity (e.g., OAB syndrome/DO, PFM dysfunction, BOO, pharmaceuticals, LUT calculi or tumours, and neurological bladder dysfunction); and (4) primary or secondary sleep disorders [589].

In postmenopausal women the relative deficiency in endogenous oestrogen production is thought to exacerbate all major pathophysiological mechanisms that may underlie nocturia [590].

*4.6.2 **Classification***

Classification of nocturia is dependent on bladder diary analysis and several parameters have been defined as important [591]:

- nocturnal urine volume – total volume of urine passed during the night (this includes the first morning void but does not include the last void prior to sleep);
- maximum voided volume – largest single voided volume in 24 hours;
- nocturia index – nocturnal urine volume divided by maximum voided volume;
- nocturnal polyuria index – nocturnal urine volume divided by 24-hour urine volume;
- nocturnal urine production – nocturnal urine volume divided by duration of sleep, in hours.

Analysis of these parameters allows clinical classification of nocturia based on physiological abnormalities that can cause nocturia:

- 24-hour polyuria;
- nocturnal polyuria;
- diminished bladder capacity;
- sleep disorders.

*4.6.3 **Diagnostic evaluation***

Evaluation of nocturia should include a thorough medical history and physical examination with particular reference to history of sleep disorders, fluid balance, associated LUTS, cardiovascular and endocrine co-morbidity, renal disease, current medications, and history of urological disease [591, 592]. There are several nocturia-specific symptom scores, such as the ICI Questionnaire-Nocturia, Nocturia Quality of Life Questionnaire (N-QoL), and Nocturia Impact Diary; some of which were developed in men. These questionnaires have shown good content and discriminant validity, reliability, and sensitivity to change as well. A further screening tool that aims to identify causes of nocturia is the Targeting the individual's Aetiology of Nocturia to Guide Outcomes (TANGO) assessment tool [593-595]. The PLANET study (PLanning Appropriate Nocturia Evaluation and Treatment) has suggested a useful tool for initial history taking called the SCREeN tool, with questions focused on evaluating areas of Sleep, Cardiovascular, Renal, Endocrine and Neurological function [596].

A bladder diary is a vital initial investigation tool in patients complaining of nocturia and further supplementary investigations are guided by any abnormalities identified. Bladder diary analysis can allow for calculation of the parameters detailed in Section 4.6.2. A low nocturnal bladder capacity or global bladder capacity will be highlighted by reduced voided volumes during nocturnal hours or both night and day. This suggests an underlying urological condition such as OAB syndrome, BOO or DU. The term 24-hour polyuria is defined as 24-hour urine production > 40 mL/kg [597] and may be present in conditions such as diabetes mellitus or diabetes insipidus. The definition of nocturnal polyuria is age dependent and the thresholds for this diagnosis range from 20% (in younger persons) to 33% (age > 65 years) of the 24-hour urine volume produced during sleep. This may also be observed in patients with loss of circadian rhythm, cardiovascular disease, sleep apnoea, or sleep disorders [591]. A large study conducted across European and American centres involving ~2,000 patients identified nocturnal polyuria as a contributory cause of nocturia in 89% of patients who were being treated for LUT abnormalities such as OAB syndrome or benign prostatic enlargement [598].

As an alternative to the ≥ 3-day bladder diary a nocturnal-only diary has been investigated in men [599]. The results showed acceptable sensitivity and specificity for the nocturnal bladder diary compared with the standard bladder diary for most parameters. The nocturnal-only diary was not able to diagnose 24-hour polyuria and has not yet been validated for use in women.

A 2022 SR and nominal group technique (NGT) consensus exercise based on fourteen observational studies of mixed populations recommended including blood tests for renal function, thyroid function, HbA1c and calcium levels in the initial work-up of patients presenting with nocturia [600-602].

Sleep disorders are potentially highly influential in nocturia, but often overlooked. A 2022 SR and NGT expert consensus based on thirteen mixed studies (nine cohort, three cross-sectional and one case-control) recommended the use of screening questions to reach a clinical diagnosis of sleep disorder (insomnia, restless legs syndrome/periodic limb movements of sleep and parasomnias) to offer conservative treatment within primary care [601].

4.6.3.1 Summary of evidence and recommendations for diagnosis of nocturia

Summary of evidence	**LE**
A thorough medical history is an integral part of the evaluation of women presenting with nocturia, including screening for sleep disorders.	4
Nocturia-specific questionnaires are sensitive to symptom changes.	3
A bladder diary allows for calculation of important indices and can identify potential causes of nocturia.	3
Nocturnal-only bladder diaries have been evaluated in men only.	3
Consider renal function, thyroid function, HbA1c and calcium level blood tests in the initial workup of women presenting with nocturia.	2

Recommendations	**Strength rating**
Take a complete medical history from women with nocturia, including screening for sleep disorders.	Strong
Use a validated questionnaire during assessment of women with nocturia and for re-evaluation during and/or after treatment.	Weak
Use a three-day bladder diary to assess nocturia in women.	Strong

Do not use nocturnal-only bladder diaries to evaluate nocturia in women.	Weak
Consider screening for sleep disorders and performing renal function, thyroid function, HbA1c and calcium level blood tests in the initial workup of women presenting with nocturia as predominant symptom.	Strong

*4.6.4 **Disease management***

When evaluating the results of trials involving treatment strategies for nocturia, it is vital to examine for clinical significance as statistical significance can be achieved with small reductions in nocturia episodes.

4.6.4.1 Conservative management

The individual components of self-management have not been critically evaluated and most recommendations are traditionally derived from consensus methodology. Interventions such as those listed below may help with nocturia but, for the majority, no quantification of their effect is possible:

- reduction of fluid intake at specific times;
- avoidance/moderation of intake of caffeine or alcohol;
- distraction techniques;
- bladder retraining;
- pelvic floor muscle training;
- reviewing medication;
- treatment of constipation.

The available data for conservative treatment of nocturia show significant heterogeneity. In a SR [582], three studies [603-605] were favourable for conservative treatment with PFMT, with another failing to confirm a benefit [606].

The highest level of evidence comes from a study of 131 patients (a secondary analysis from a prospective RCT that had urgency-predominant UI as the primary inclusion criterion). The study found that training in PFM contraction, which included four sessions of biofeedback-assisted PFMT, reduced nocturia by a median 0.50 episodes per night and was significantly more effective than anticholinergic drug treatment or placebo [603]. The certainty of evidence associated with this treatment is moderate.

A smaller RCT of 50 women with urinary complaints, randomised 1:1 to BT and PFMT compared with a control group receiving no treatment, showed a significant decrease in patients' complaints of nocturia [604]. Another RCT in only 24 women compared PFMT only to Interferential Therapy plus [605]. Although the authors did not find significant differences between the groups, the change in nocturia episodes before and after treatment was statistically significant in both groups. This study was underpowered by the authors' own admission. The level of certainty of the evidence from these two trials is low. A large randomised, two-arm, parallel design, superiority trial (n = 647; women), compared the effects of unsupervised behavioural PFMT programmes delivered in a two-hour class format and 20 minutes video format on UI prevention. No significant between-group differences of nocturia were observed at 3 months and 12 months, but at 24 months, women in the 2 hour class group were less likely to have fewer nocturia episodes (OR = 0.5; 95 % CI: 0.3–0.7; p = 0.005) compared with those in the 20 minutes video group, but the authors concluded that the evidence is not sufficient to support one management strategy [605].

A multicentre, open-labelled, RCT evaluated whether cognitive behavioural therapy (CBT) using a self-assessment via a checklist is effective in improving nocturia in a mixed population (30/78 women). The mean rate of achievement of the CBT group was 64.4%. There was no significant difference between the two groups in night-time frequency based on the IPSS Q7 at four weeks but episodes of nocturia on the frequency volume chart (FVC) were significantly smaller in the CBT group (1.9 ± 0.9) than in the control group (2.4 ± 1.3; p = 0.039) [607].

In a secondary analysis from a prospective RCT, 210 women with urgency UI (UUI) were evaluated for change from baseline in the number of episodes of nocturia and nocturnal incontinence between groups allocated to medical treatment (tolterodine ER 4 mg) alone vs. medical treatment plus PFMT [606]. No significant difference between the groups was found and the actual difference in nocturia episodes in either treatment arm was small. The level of certainty of the evidence from this trial is low.

A recent RCT has explored both individual and group PFMT with a specific secondary outcome of number of patients with two or more nocturia episodes per night [319]. The authors reported similar reductions, with > 30% of patients who had ≥ 2 episodes of nocturia at baseline no longer experiencing this level of symptoms at one year after PFMT.

One small, single-centre RCT in which functional magnetic stimulation was compared with no treatment in 39 women reported a significant decrease in nocturia (together with voiding frequency and pad use) in the treatment group compared with the control group [608].

In patients with obstructive sleep apnoea who complain of nocturia, continuous positive airway pressure has been shown to be effective in a SR and meta-analysis of five RCTs involving both sexes [609]. This treatment was associated with an average numerical reduction in nocturia of > 2 episodes per night.

4.6.4.1.1 Summary of evidence and recommendations for conservative management of nocturia

Summary of evidence	**LE**
Individual or group PFMT appears to be equally effective for reduction in nocturia episodes.	1b
Most studies evaluating PFMT for nocturia in women with additional urinary symptoms have shown positive results compared with placebo or anticholinergic drugs.	1b
Treatment of nocturia secondary to obstructive sleep apnoea with continuous positive airway pressure reduces nocturia episodes.	1a

Recommendations	**Strength rating**
Offer women with lower urinary tract symptoms (LUTS) lifestyle advice prior to, or concurrent with, treatment.	Strong
Offer pelvic floor muscle training for nocturia (either individually or in the group setting) to women with urinary incontinence or other storage LUTS.	Strong
Offer women with nocturia and a history suggestive of obstructive sleep apnoea a referral to a sleep clinic for assessment of suitability for continuous positive airway pressure treatment.	Strong

4.6.4.2 Pharmacological management

4.6.4.2.1 Desmopressin

Desmopressin is a synthetic analogue of the hormone vasopressin and is most often used for management of nocturia due to nocturnal polyuria. In a SR [582], three trials specifically conducted in women were found but more additional data could be extracted from studies in mixed populations. The earliest evidence comes from a 1982 single-site crossover trial involving 25 women treated with 20 g desmopressin or placebo and revealed a significant decrease in nocturnal urine output at six weeks [610]. A more recent multicentre, multinational double-blind RCT involving 141 women used desmopressin 0.1, 0.2 or 0.4 mg orally at bedtime after a dose-titration period [611]. This increased the likelihood of a positive outcome because non-responders were excluded at that stage. At three weeks, significant reductions in nocturnal urinary frequency and nocturnal diuresis were reported. In another multicentre double-blind RCT, 58 women were randomised into five groups (twelve receiving placebo, twelve desmopressin 10 µg, eleven desmopressin 25 µg, eleven desmopressin 50 µg and twelve desmopressin 100 µg) for four weeks [612]. A dose–response relationship was observed, and women appeared more sensitive than men to desmopressin. Significant changes in nocturnal urine volumes were reported in favour of the higher desmopressin doses. Differences in the nocturnal polyuria index also tended to favour desmopressin over placebo and the higher desmopressin doses. The level of certainty of the evidence from these trials is low.

Desmopressin can be safely combined with anticholinergics with significant benefit in women with OAB and nocturnal polyuria, as shown by a multicentre RCT of 97 patients [613]. A *post hoc* analysis of data comparing three-month once-daily combination (desmopressin 25 µg/tolterodine 4 mg, n = 49) or monotherapy (tolterodine 4 mg/placebo, n = 57) revealed a significant reduction in nocturnal void volume and time to first nocturnal void in favour of combination therapy. The level of certainty of the evidence from this trial is moderate.

Pooled data from three RCTs were used to examine the adverse event profile of desmopressin, specifically hyponatraemia [614]. The authors reported that the majority tolerate desmopressin treatment without clinically significant hyponatraemia, but risk increased with age and lower baseline serum sodium concentration. They advised that desmopressin treatment in elderly patients should include careful monitoring of the serum sodium concentration and should be avoided in patients with a baseline serum sodium concentration below normal range.

4.6.4.2.2 Anticholinergics

A SR [582] identified three RCTs involving anticholinergics such as oxybutynin 2.5 mg/day [603] and tolterodine 4 mg/day [606, 613]. A secondary analysis from a prospective RCT involving 131 women with nocturia followed up for eight weeks found that women receiving 2.5 mg immediate-release oxybutynin once daily (with the possibility of self-titration and dose escalation to 5 mg three times daily) had fewer nocturia episodes than women receiving placebo [603]. Women receiving oxybutynin plus behavioural therapy also exhibited a significant decrease in nocturia episodes compared with placebo and oxybutynin alone. A multicentre RCT with 305 women followed up for eight weeks examined the efficacy of tolterodine tartrate 4 mg alone or in combination with behavioural training [606]. Significant differences compared with baseline were observed in mean nocturia episodes and nocturnal incontinence episodes in both groups, but no difference was reported between the two treatment groups. The level of certainty of the evidence from this trial is moderate.

In an RCT including 97 women with nocturnal polyuria and OAB syndrome, comparing three months of once daily combination (desmopressin 25 µg/tolterodine 4 mg, n = 49) or monotherapy (tolterodine 4 mg/placebo, n = 57), a significant reduction in mean number of nocturnal voids compared with baseline was reported in both groups [613]. The level of certainty of the evidence from this trial is moderate.

A large comparative study followed 407 women with OAB and nocturia for four weeks [615]. The patients were given tolterodine as monotherapy in one group, and tolterodine combined with estazolam (a benzodiazepine) in the other group. Significant changes from baseline in both groups for the main outcome of number of nocturia episodes were reported. Combination therapy showed a significant benefit for women with OAB and nocturia compared with monotherapy in terms of differences in number of nocturia episodes, urgency episodes in 24 hours, UUI episodes in 24 hours, and voided volume per micturition. The level of certainty of the evidence from this trial is very low.

A small multicentre RCT compared oxybutynin patch vs. mirabegron on nocturia-related QoL in women with OAB. Both treatments showed improvements in N-QoL score at four weeks, but mirabegron showed statistical differences at eight weeks. Additionally, only mirabegron decreased nocturnal frequency and water intake, and prolonged hours of uninterrupted sleep eight weeks after administration with statistical significance, whereas oxybutynin patch did not [616].

4.6.4.2.3 Oestrogens

In a SR [582], only a single RCT investigating the efficacy of oestrogen for nocturia was identified [617]. This trial compared an oestradiol-releasing vaginal ring with an oestriol vaginal pessary in 251 women followed up for six months. There was no difference between the treatment groups in the number of women reporting nocturia, although they reported significant change from baseline in both treatment arms with > 50% of subjects responding in each arm. The certainty of evidence for this outcome was low.

4.6.4.2.4 Diuretic treatment

In a randomised placebo-controlled study an afternoon dose of 40 mg furosemide (taken six hours before bedtime) in an attempt to establish complete diuresis before bedtime was given to elderly men [618]. In the 43 men who completed the study, night-time frequency in the furosemide group fell by 0.5 episodes compared with placebo, and percentage night-time voided volume fell by 18%. No such study has been carried out in female patients.

4.6.4.3 Summary of evidence and recommendations for pharmacological management of nocturia

Summary of evidence	**LE**
Desmopressin treatment for nocturia shows significant reductions in nocturnal urine output, nocturnal urinary frequency, and nocturnal polyuria index.	1b
Most nocturia patients tolerate desmopressin treatment without clinically significant hyponatraemia; however, the risk increases with increasing age and decreasing baseline serum sodium concentration.	1a
Treatment of nocturia in OAB patients with anticholinergic drugs shows reduction in nocturia episodes.	1b
Combination of PFMT and anticholinergics does not appear to confer additional benefit over anticholinergics alone.	1b
Combination of anticholinergic and desmopressin treatment appears to reduce nocturnal voided volume and time to first nocturnal void in women with nocturnal polyuria.	1b
Vaginal oestrogen may be beneficial in the treatment of nocturia in around 50% of women.	1b

Afternoon (timed) diuretic treatment with furosemide reduces nocturia episodes and nocturnal voided volume in men but no similar studies have been conducted in women.	1b
Assessment of clinical significance is important when evaluating trials involving treatment strategies for nocturia, as statistical significance can be achieved with small reductions in nocturia episodes.	3

Recommendations	Strength rating
Offer desmopressin treatment for nocturia secondary to nocturnal polyuria to women, following appropriate counselling regarding the potential benefits and associated risks (including hyponatraemia).	Strong
Carefully monitor serum sodium concentration in elderly patients treated with desmopressin. Avoid prescribing desmopressin to patients with a baseline serum sodium concentration below normal range.	Strong
Offer anticholinergic treatment for nocturia to women with urge urinary incontinence or other LUTS, following appropriate counselling regarding the potential benefits and associated risks.	Strong
Inform women with nocturia that combination of behavioural therapy and anticholinergic drugs is unlikely to provide increased efficacy compared with either modality alone.	Weak
Offer combination of anticholinergics and desmopressin to women with overactive bladder and nocturia secondary to nocturnal polyuria, following appropriate counselling regarding the potential benefits and associated risks.	Weak
Offer vaginal oestrogen treatment to women with nocturia, following appropriate counselling regarding the potential benefits and associated risks.	Weak
Offer timed diuretic treatment to women with nocturia secondary to polyuria, following appropriate counselling regarding the potential benefits and associated risks.	Weak

4.6.4.4 Surgical management

Surgical treatment is generally reserved for those with underlying correctable LUT disorders. The effect of surgical treatments on symptoms of nocturia can be found in the relevant condition-specific sections of this guideline.

*4.6.5 **Follow-up***

Follow-up of patients with nocturia is dependent on the underlying aetiology of this symptom and the treatment given.

4.7 Pelvic organ prolapse and lower urinary tract symptoms

*4.7.1 **Epidemiology, aetiology, pathophysiology***

Pelvic organ prolapse is a common condition in adult women. The prevalence of POP is 3–6% when bothersome symptoms are used to characterise the condition and increases to 50% when a purely anatomical definition is used [619].

The estimated lifetime risk for POP surgery is 12.6% [620]. Parity, vaginal delivery, ageing, and obesity are the most commonly recognised risk factors [621].

Although the aetiology of POP is not fully understood, birth trauma to the levator ani complex is recognised as central to its development. In normal physiology, an intact levator ani complex functionally closes the genital hiatus surrounding the vagina, limiting the pressure gradient between the intra-abdominal and intravaginal areas. During physical activities, this reduces stress on the endopelvic fascia and its condensations (e.g., ligaments), which are crucial in securing the bladder, uterus, and rectum to their surroundings. Current aetiological concepts include widening of the levator hiatus due to birth trauma, which creates a low-pressure area in the vagina and consequently increased stress on the ligaments, fascial elements, and PFMs during physical activity. When the supporting function of the muscles and connective tissues fails, POP may develop [622]. This concept also explains the time lapse between birth trauma and occurrence of POP.

Pelvic organ prolapse and LUTS often occur simultaneously in women. In isolation, both POP and LUTS are prevalent conditions in women, although the prevalence of LUTS in women with POP exceeds that of LUTS in women without POP [619]. In a meta-analysis and SR, consistent results demonstrated a higher prevalence of OAB symptoms and UUI in patients with POP than without POP [619, 623]. The observation that LUTS may improve or worsen after POP treatment suggests a link between these two entities [619]. Clinical examples include the occurrence of BOO symptoms in severe POP, and disappearance of SUI symptoms with progression

of POP (and conversely the occurrence of SUI after treatment of POP) [624]. Pelvic organ prolapse is also associated with symptoms of bowel and/or sexual dysfunction [625].

*4.7.2 **Classification***

Since 1996, POP has been classified according to the Pelvic Organ Prolapse-Quantification (POP-Q) system [626]. For specifics on how to perform the POP-Q measurement and the nine standard points to be measured (Figures 2 and 3), we refer to the original publications [626, 627].

The vagina is divided into anterior (bladder), posterior (rectum) and apical (cervix or vaginal vault) compartments. After scoring the position of the nine POP-Q points, a prolapse of each compartment is graded numerically from stage 0 to 4, with stage 0 being no prolapse and stage 4 being complete eversion of the compartment. A crucial marker in staging POP is the hymenal remnant. Any POP with a maximum descent that is still 1 cm above the hymen (e.g., in the vagina) is considered a stage 1 POP. A maximum descent between 1 cm above and 1 cm below (outside the vagina) the hymen is a stage 2 POP. Any descent beyond 1 cm below the hymen is a stage 3 POP.

The figures below show the POP-Q staging in comparison to the Baden–Walker system (and others) used before the international consensus on the POP-Q staging was introduced as the new standard.

Figure 2: Prolapse classification system

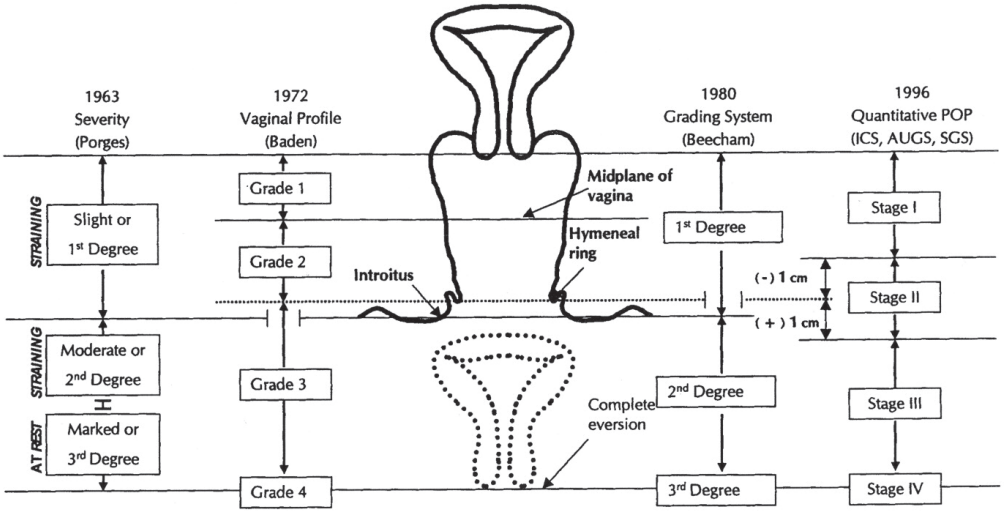

Figure reproduced with permission from the publisher, from Theofratus et al. [627].

Figure: 3: Pelvic Organ Prolapse-Quantification staging

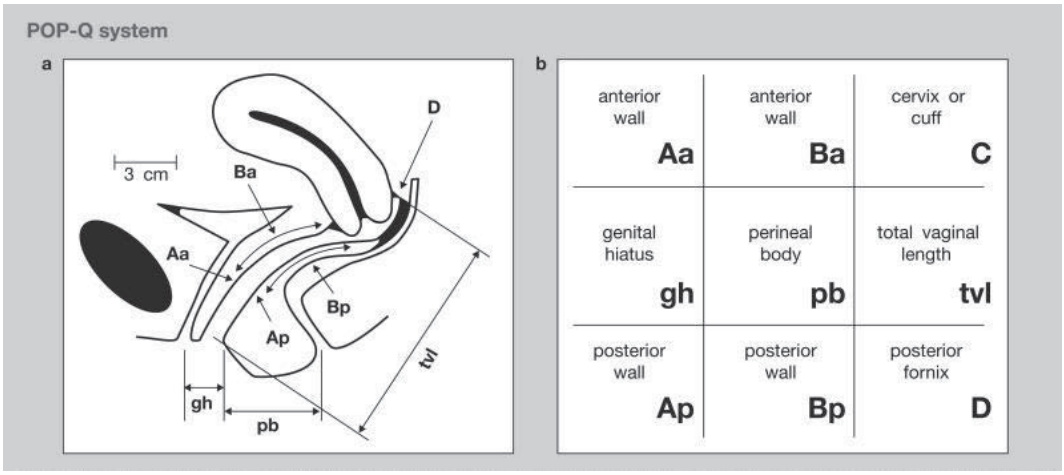

Figure reproduced with permission from the publisher, from Bump et al. [626]. The standardisation of terminology of female POP and pelvic floor dysfunction.

*4.7.3 **Diagnostic evaluation***

Pelvic organ prolapse is a clinical diagnosis and is staged according to the POP-Q system. Pelvic organ prolapse that is above the hymen should only produce mild symptoms at most [628]. In cases where there is a discrepancy between the clinical symptoms and POP-Q staging, it is advised to consider performing the POP-Q measurement in a standing rather than supine position or re-evaluating at a later time in the day. Magnetic resonance imaging assessment demonstrated a marked difference in POP staging between supine and standing position [629]. Additional diagnostic tests for POP are mainly indicated if there are accompanying symptoms like LUTS or bowel dysfunction. Imaging techniques are not advised for the routine diagnostic work-up of patients presenting with POP [66]. The role of urodynamics in the diagnostic work-up of SUI has been discussed in Section 4.2, of this guideline.

The use of techniques to reduce POP during urodynamic evaluation to diagnose occult SUI is common practice. This information may be used to decide if additional anti-UI surgery should be offered at the time of POP surgery or to counsel patients on the possible after-effects of POP treatment.

There are several POP reduction methods that may be used during physical examination or urodynamic evaluation. In a multicentre observational study, five different cough/stress tests were compared for their ability to detect SUI in women with POP [630]. Stress urinary incontinence during at least one of the five tests occurred in 60/205 (29.2%) women without SUI symptoms. Looking at single test performance, the detection rate of occult SUI in women without symptoms increased from 4.4% in case of no reduction to 22% in case of reduction with a pessary.

A large RCT included women with POP without symptoms of SUI, who were randomised to sacro-colpopexy with or without Burch colposuspension [631]. Three hundred and twenty-two stress-continent women with stages 2–4 prolapse underwent standardised urodynamic testing, and the protocol included five prolapse reduction methods. Preoperatively, twelve of 313 (3.7%) women demonstrated urodynamic SUI without prolapse reduction. Preoperative detection of urodynamic SUI with prolapse reduction at 300 mL was by pessary, 6% (5/88); manual, 16% (19/122); forceps, 21% (21/98); swab, 20% (32/158); and speculum, 30% (35/118). Another large trial included women with POP without SUI symptoms randomised to vaginal POP surgery with or without (sham incision) MUS [632]. Before surgery, 33.5% (111/331) of women demonstrated SUI at a prolapse-reduction cough stress test. In an observational study of 172 women with POP without SUI, 19% of women were diagnosed with occult SUI by basic office evaluation (with prolapse reduction with swab on forceps) and 29% on urodynamic evaluation [633].

In summary, SUI can be demonstrated in women with POP without symptoms of SUI after POP reduction in up to 30% of cases. There is no consensus on the best reduction technique.

Although the detection rate of occult SUI increases after reduction of POP in women without SUI symptoms, its clinical value is under debate.

In one trial, preoperative stress-continent women were evaluated during urodynamic testing with prolapse reduction to determine if they were more likely to report postoperative SUI, regardless of concomitant colposuspension (controls 58% vs. 38% and Burch colposuspension 32% vs. 21%) [631]. In another trial, women with SUI during the cough stress test after POP reduction reported UI at three months in 29.6% in the synthetic MUS group, compared with 71.9% in the sham group [632]. Women with a positive prolapse reduction stress test before surgery appeared to receive more benefit from a synthetic MUS at three months, but not at twelve months, than did those with a negative test.

In a large observational study, women did not receive additional anti-UI surgery even if they had SUI after POP reduction preoperatively. In this scenario, 9% (16/172) of women developed postoperative *de novo* SUI and six underwent surgery for *de novo* SUI [633]. Women with demonstrable preoperative SUI were more at risk of postoperative SUI: 28% vs. 5%. Based on urodynamic evaluation only, one more woman was predicted to have postoperative SUI, but all six women who underwent treatment for *de novo* SUI showed SUI during basic office evaluation.

In a model developed to predict the risk of *de novo* SUI in women undergoing POP surgery based on findings from two trials, twelve preoperative predictors were tested [634]. Positive SUI during a preoperative prolapse reduction test was included in this model, but it failed to be a significant predictor as a single item. Preoperative POP stage was not associated with risk of *de novo* SUI.

4.7.3.1 Summary of evidence and recommendation for detection of SUI in women with POP

Summary of evidence	LE
Pelvic organ prolapse reduction during cough stress test, in office or during urodynamics detects SUI in ~30% of continent women.	2a
Women with SUI after POP reduction preoperatively (occult SUI) is likely to be at increased risk of developing SUI symptoms after POP surgery.	2a

Recommendation	Strength rating
Perform pelvic organ prolapse (POP) reduction test in continent women to identify those with occult stress urinary incontinence and counsel them about the pros and cons of additional anti-incontinence surgery at the time of POP surgery.	Strong

4.7.3.2 Urodynamics in women with pelvic organ prolapse and LUTS (without stress urinary incontinence)
The role of urodynamics is less clear in women presenting with POP and concurrent LUTS, other than SUI. Pelvic organ prolapse is a complex condition incorporating different compartments of the vagina and presenting at different stages of severity. Information about detrusor activity, as assessed with urodynamics, may provide information about the risk of developing DO after surgery, but also on the risk of urinary retention due to DU. An observational study assessed predictors for DO following POP surgery for POP-Q stage 3 or higher in 1,503 women and the authors concluded that preoperative maximum urethral closure pressure > 60 cm H2O, Qmax < 15 mL/s, maximum detrusor voiding pressure (D_{max}) ≥ 20 cm H_2O and PVR volume ≥ 200 mL were independent risk factors for postoperative DO [635]. A small observational study (n = 49) evaluated patients with preoperative DU (detrusor pressure at maximum flow was ≤ 10 cm H_2O and Q_{max} ≤ 12 mL/s) after POP surgery. Surgery objectively cured DU in 47% of women and urodynamic findings normalised after surgery [636]. The 2019 NICE Guidelines do not include a recommendation to perform urodynamics as part of the diagnostic work-up of POP, except for combination with symptomatic SUI [66].

4.7.4 ***Disease management***
Pelvic organ prolapse symptoms can be treated with PFMT, vaginal pessary, surgery, or a combination of these treatments. The scope of these guidelines is to focus on LUTS in women; therefore, only data on the effect of treatment of urinary symptoms are presented.

4.7.4.1 Conservative management of pelvic organ prolapse
The 2013 NICE guidelines on Urinary Incontinence and POP in Women had an updated management section in 2019, including a full evidence review [66]. The overall conclusion with respect to conservative treatment for POP was that the evidence is of low quality. Thirteen RCTs were identified. Seven studies presented data on changes in urinary symptoms [637-643]. An additional search identified four RCTs that addressed the addition of PFMT to POP surgery [644-647], and one that compared combined PFMT/Pilates therapy with lifestyle advice by leaflet [648].

Five studies [638, 640-642, 648] compared PFMT to lifestyle advice/leaflet; one study [639] compared PFMT alone to PFMT with pessary; one study [643] compared PFMT to pessary therapy; and five studies compared surgery for POP with or without addition of PFMT [637, 644-647].

4.7.4.1.1 Pelvic floor muscle training versus lifestyle advice
An RCT (n = 109) reported that, at six months' follow-up, the ICIQ-UI-SF scores improved in favour of the PFMT group (2.40 points) compared with a control group receiving lifestyle advice only (0.2 points), but the mean baseline score in the PFMT group was higher than in the control group (7.4 vs. 5.9) [638]. Likewise, it has to be noted that the absolute ICIQ-UI-SF values at six months' follow-up were not significantly different between PFMT (4.8) and controls (5.2).

Two publications from one RCT reported on the three-, six- and twelve-month results of lifestyle advice only vs. lifestyle advice combined with group PFMT [640, 641]. The Urogenital Distress Inventory-6 (UDI-6) and Urinary Impact Questionnaire-7 (UIQ-7) questionnaires were used to assess urinary symptoms. At three months' follow-up, both groups (53 women in the lifestyle group and 56 in the lifestyle + PFMT cohort) reported significantly improved UDI-6 scores, while the lifestyle-only group also reported significantly greater improvement in the UIQ-7 score. Between-group comparison showed no differences in UDI-6 and UIQ-7 scores at six months. At twelve months' follow-up, the majority of women had sought additional treatment (70% in the lifestyle-only group

and 48% in the lifestyle/PFMT group). The number of patients remaining on the original therapy was too small to reach strong conclusions.

One RCT reported on six- and twelve-months follow-up of 225 women with POP-Q stage 1–3 randomised to individualised PFMT and 222 women randomised to lifestyle leaflet information only (control) [642]. At six months, significantly more women in the control group reported UI, the need to strain to empty their bladder, and the feeling of incomplete emptying compared to the PFMT group. ICIQ-SF score was also significantly worse in the control group as compared to the PFMT group. However, at twelve months, there was no significant difference in these items between groups. It has to be noted that 50% in the control group received additional treatment within the twelve-month study period. Twenty-seven percent had additional PFMT, which may have had an effect on the twelve-month data.

Another RCT reported on the 24-month follow-up of 414 women with stage 1–3 POP (207 assigned to PFMT/Pilates and 207 to lifestyle advice) [648]. Urinary symptoms were assessed with the ICIQ-UI-SF and a question about UI and difficulty emptying the bladder. At 24 months, the ICIQ-UI-SF score was significantly better in the intervention group (mean difference −0.83). However, the proportion of women reporting any UI did not differ between the groups, nor did the number of pads used weekly.

One RCT compared PFMT alone to PFMT and pessary for symptomatic POP [639]. Urinary tract symptom changes were assessed using UDI-6 and UIQ at six and twelve months follow-up. At twelve months, there was no difference in the between-group comparison. With respect to the UIQ, women in the pessary/PFMT group showed a significant improvement from baseline, but the PFMT-only group did not. Women in the pessary/PFMT group reported significantly more frequent *de novo* SUI (48% vs. 22%), and more improvement of pre-existing voiding difficulty (62.5% vs. 35.5%).

4.7.4.1.2 Pelvic floor muscle training versus pessary only

One RCT reported on the 24-month follow-up of 82 women with symptomatic POP randomised to pessary therapy and 80 women randomised to PFMT [649]. Both in the ITT and per protocol analyses, the UDI-6 score did not differ significantly between groups at 24 months of follow-up.

4.7.4.1.3 Surgery alone versus surgery with pelvic floor muscle training

An assessor blinded RCT compared surgery for POP with or without additional pre-and postoperative PFMT. At twelve months after surgery, there were no significant differences between the groups on the change in scores of the UDI nor the IIQ scores [637].

Another RCT reported on the six-month follow-up of 57 women (28 surgery/29 surgery with PFMT). There was a significant improvement in the UDI-6 score for both groups, but not between groups [645].

Another RCT reported on the results of a 2x2 factorial design in which women were first randomised between two surgical techniques for POP and between additional PFMT (n = 188) or not (n = 186) [646]. The UDI was used to assess urinary symptoms up to 24 months. No significant differences were found between the addition of PFMT to surgery or not. Another study of the same population reported on SUI in particular [647]. No significant differences were found between women who had additional PFMT and those who had not.

In 2020 an RCT reported on 40- and 90-days follow-up of 48 women randomised to supervised PFMT before and after surgery and 40 women having surgery only [644]. No significant differences in UDI-6 scores were identified at 40 and 90 days.

ICI 2017 [18] concluded that there is level 1a evidence that PFMT reduces pelvic floor symptoms in women with POP, there is some evidence that it reduces POP specific symptoms like bulging. Some RCTs also show an improvement in POP stage with PFMT [650]. The NICE guidelines on the management of POP advocate considering supervised PFMT for ≥ 16 weeks as initial treatment for symptomatic prolapse [66]. The use of pessary is also to be considered, alone or combined with PFMT. It is important to recognise that a benefit is expected on typical POP symptoms, like feeling or seeing a bulge out of the vagina, and not on LUTS, as the reported RCTs showed. From a urological perspective, initiating conservative treatment for asymptomatic POP in order to treat UI or bladder emptying problems is not supported by the data.

4.7.4.1.4 Pessary versus surgery alone

A prospective cohort study showed that surgery in comparison with pessary treatment resulted in statistically significant more women reporting subjective improvement [651].

4.7.4.1.5 Summary of evidence and recommendation for the conservative treatment of pelvic organ prolapse and lower urinary tract symptoms

Summary of evidence	LE
Pelvic floor muscle training improves LUTS for up to 6 months in POP patients who do not have additional pessary or surgical treatment.	2a
If pessary therapy or surgical intervention is used for POP, PFMT does not show an additional benefit.	2a

Recommendations	Strength rating
Inform women with pelvic organ prolapse (POP), who do not need a vaginal pessary or surgical intervention, about the potential relief from lower urinary tract symptoms (LUTS) from pelvic floor muscle training (PFMT).	Strong
Do not offer preoperative PFMT to improve outcome of LUTS if pessary therapy or surgical intervention is indicated for POP.	Strong

4.7.4.2 Pelvic organ prolapse surgery and overactive bladder

Only a few studies have specifically addressed the effect of POP surgery on OAB symptoms. A SR of twelve studies, excluding women with SUI, evaluated OAB symptoms before and after surgery [623]. All but one study reported improvement of OAB symptoms. The same authors performed a prospective analysis of 505 women who had POP surgery with or without mesh [652]. Mean follow-up was 12.7 months. The incidence of bothersome urinary frequency reduced from 36.6% to 14.6%, with *de novo* symptoms occurring in 6.1%. Bothersome urgency symptoms reduced in 36.8% to 12.9% of women, with 5.0% developing *de novo* symptoms. Urge urinary incontinence symptoms reduced from 21.2% to 6.1% of women, with 5.3% developing *de novo* symptoms.

One observational study evaluated frequency and urgency symptoms without consideration of bother in 87 women undergoing POP surgery and showed an improvement in frequency by 75%, and in urgency in 83% [653]. The effect of the POP-Q stage did not seem to influence the effect of surgery on OAB symptoms [652, 653].

Another observational study (n = 43) evaluated the effect of posterior repair on OAB/DO and showed a 70–75% improvement rate in both parameters after surgery [654].

4.7.4.3 Pelvic organ prolapse surgery and bladder outlet obstruction

The criteria for BOO are based on urodynamic assessment. POP can be categorised as anatomical BOO, which is addressed in Sections 4.5.2.2 and 4.5.3.1.

4.7.4.4 Pelvic organ prolapse surgery and stress urinary incontinence

The aim of this section is to address the options available to women who require surgery for POP and who have associated SUI (either before or after reduction of prolapse), and to assess the value of prophylactic anti-UI surgery in women with no evidence of SUI.

A SR and meta-analysis of ten trials on prolapse surgery with or without an anti-incontinence procedure was reported in 2018 [655]. In addition, a Cochrane review including nineteen trials (n = 2,717) evaluating bladder function after surgery for POP presented analyses of women with POP and SUI, women with POP and occult SUI, and women with POP who were continent [656].

4.7.4.4.1 Vaginal pelvic organ prolapse surgery in women with stress urinary incontinence

Two trials addressed postoperative SUI in patients who had been diagnosed with SUI preoperatively and had vaginal POP surgery [657, 658]. Two trials (n = 185 and 134) compared the use of MUS at initial POP surgery to POP surgery alone. The RR for postoperative SUI was 0.30 in favour of the combined POP surgery and MUS group. One of these two trials also compared the use of MUS at initial POP surgery and at three months if SUI persisted [657]. At twelve months' follow-up, there was no difference between the groups regarding postoperative UI (RR 0.41); however, 44% of the women without initial MUS never required surgery and 29% were dry.

4.7.4.4.2 Abdominal pelvic organ prolapse surgery in women with stress urinary incontinence

One RCT randomised 47 women with POP and SUI to an abdominal POP surgical procedure, e.g., sacro-colpopexy with or without Burch colposuspension. Additional SUI surgery did not improve postoperative SUI as compared to sacro-colpopexy alone (RR: 1.38) [659]. This finding remained consistent over five years' follow-up

[660]. Another RCT compared the addition of a MUS or Burch colposuspension to an abdominal sacro-colpopexy in 113 women with POP and SUI [661]. At two years' follow-up, the RR for postoperative SUI was 0.54 in favour of the MUS group.

4.7.4.5 Vaginal pelvic organ prolapse surgery in continent women

One RCT compared vaginal POP surgery alone with concomitant POP surgery and MUS in 220 women. Postoperative SUI occurred in 46/113 (40.7%) women who had POP surgery alone, compared to 30/107 (28.0%) who had additional MUS (RR: 0.69) [656].

4.7.4.5.1 Abdominal pelvic organ prolapse surgery in continent women

Two RCTs compared abdominal sacro-colpopexy with (n = 180) or without (n = 187) Burch colposuspension with an outcome favouring the addition of Burch colposuspension (RR for *de novo* SUI: 0.69) [659, 662]. However, 34% of women in the prophylactic Burch colposuspension group developed *de novo* SUI (as compared to 49% in the control group). An RCT with medium-term follow-up (mean 39.5 months) showed that additional SUI surgery was needed by only 1/31 women (3%) in both groups [660, 663].

4.7.4.5.2 Vaginal pelvic organ prolapse surgery in women with prolapse and occult stress urinary incontinence

Five RCTs including a total of 194 women who had vaginal POP repair alone and 174 women who had an additional MUS at the time of primary surgery were identified [632, 664-667]. The RR of postoperative SUI was 0.38 in favour of the MUS group.

4.7.4.6 Adverse events associated with combined pelvic organ prolapse and stress urinary incontinence surgery

Data from six RCTs on vaginal POP surgery with MUS were pooled to assess adverse events [632, 657, 658, 665-667]. Urgency urinary incontinence was less frequent after combination surgery as compared to POP surgery alone (28% vs. 42%; RR: 0.7), but there was a tendency towards more voiding problems. Adverse events directly related to surgery occurred more often in the combination group (28% vs. 15%; RR: 1.8), as did serious adverse events such as bladder perforation, urethral injuries, and tape exposure (14% vs. 8%; RR: 1.7) [655].

In summary, it is difficult to generalise the results of trials using different procedures to treat both POP and UI. It seems that with a combined procedure, the rate of postoperative SUI is lower but voiding symptoms and complication rates are higher. Studies using MUS have shown more significant differences in UI outcomes with combined procedures than when other types of anti-UI procedure have been used. It must be taken into account that although more women are dry after combined surgery for POP with MUS, there are potential adverse events that should be balanced against potential benefits.

4.7.5 Summary of evidence and recommendations for surgery in women with both pelvic organ prolapse and stress urinary incontinence

Summary of evidence	**LE**
Women with POP and UI	
Surgery for POP and 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 and SUI vs. POP surgery alone.	1a
Combined surgery for POP + SUI carries a higher risk of adverse events than POP surgery alone.	1a
Continent women with POP	
Continent women with POP are at risk of developing SUI postoperatively.	1a
Women with POP and OAB	
There is some low-level inconsistent evidence to suggest that surgical repair of POP can improve symptoms of OAB.	2b

Recommendations for women requiring surgery for bothersome pelvic organ prolapse (POP) who have symptomatic or occult stress urinary incontinence (SUI)	**Strength rating**
Offer simultaneous surgery for POP and SUI only after a full discussion of the potential risks and benefits of combined surgery vs. POP surgery alone.	Strong

Inform women of the increased risk of adverse events with combined prolapse and anti-urinary incontinence surgery compared to prolapse surgery alone.	Strong
Recommendations for women requiring surgery for bothersome POP who do not have symptomatic or occult SUI	
Inform women that there is a risk of developing *de novo* SUI after prolapse surgery.	Strong
Do not offer concomitant anti-incontinence surgery at the time of abdominal prolapse surgery.	Strong

4.8 Urinary fistula

The evidence relating to diagnosis and treatment of urinary fistulae is generally low level and largely composed of case series and other consensus statements. In particular, the epidemiology, aetiology, diagnosis, treatment and prevention of obstetric and non-obstetric fistulae have been described in detail during the 2016 ICI conference [668]. Most non-obstetric fistulae are iatrogenic in origin, caused by pelvic surgery (e.g., hysterectomy for benign or malignant conditions, bowel resection, and urological surgery). The risks during pelvic surgery increase proportionally to the complexity of the resection, the extent of the primary disease, and with a past history of radiotherapy (especially for recurrent disease). When a fistula occurs following radiotherapy for primary treatment, this may be an indication of tumour recurrence.

*4.8.1 **Epidemiology, aetiology and pathophysiology***

4.8.1.1 Obstetric fistula

According to the WHO, fistulae affect > 2 million women, mostly from sub-Saharan African and Asian countries. The pooled prevalence of fistula from population studies is 0.29/1000 pregnancies [669]. Poor quality obstetric care, staff unaccountability, late referral, and poor nursing standards have been identified as health system causes [669]. However, obstructed labour is poorly documented. The main individual risk factors include age at first marriage, short stature, pregnancy with a male child, failure to attend antenatal care, low socio-economic status, low social class, lack of employment, and illiteracy [670-672]. Obstetric fistulae have detrimental consequences on global and individual health and are associated with malnutrition, sexual dysfunction, anxiety, depression, insomnia, social isolation, worsening poverty, and suicide [673, 674].

4.8.1.2 Iatrogenic fistula

Poor obstetric care is usually responsible for VVFs in the developing world. By contrast, in the developed world, gynaecological or pelvic surgery is the main cause of VVF. In a recent French epidemiological study, pelvic surgery accounted for two thirds of VVF causes [675].

4.8.1.2.1 Post-gynaecological surgery

An injury to the urinary tract during hysterectomy for benign conditions (60–75%), hysterectomy for malignant conditions (30%) and caesarean section (6%) are the main causes of postoperative VVF in the developed world [676, 677]. The risk of pelvic organ fistula following hysterectomy ranges from 0.1-4% [678].

Fistulae may also occur as a result of primary or recurrent malignancy, or as a consequence of cancer treatment by surgery, radiotherapy, and/or chemotherapy.

In a study including 536 women undergoing radical hysterectomy for invasive cervical cancer, bladder injury occurred in 1.5% with VVFs forming in 2.6% and uretero-vaginal fistulae (UVFs) in 2.4% of cases [679]. Overall, the rate of urogenital fistula appears to be ~9 times higher following radical hysterectomy for malignant disease as compared to that following simple hysterectomy (abdominal or vaginal for benign conditions) [680]. Bladder-sparing techniques during pelvic exenteration can increase the risk of fistula formation [681].

4.8.1.2.2 Radiation fistula

The risk of fistula seems to be higher for postoperative external beam radiation (1.9%) compared to intravaginal brachytherapy (0.8%) [682], without any predictive factor being identified [683]. This is most likely due to the heterogeneity of data regarding the tumour type and stage, the form of radiation, and the site and dose delivered.

4.8.1.2.3 Rare causes of vesico-vaginal fistula

Foreign bodies such as pessaries, sex toys, cups etc. can be a cause of delayed presentation of VVF [684-686]. Ketamine abuse has also been shown to be responsible for fistula formation [687].

4.8.1.3 Summary of evidence for epidemiology, aetiology, and pathophysiology of urinary fistula

Summary of evidence	LE
The risk of injury to the urinary tract and subsequent fistula formation is higher in women with malignant disease undergoing radical surgery than in women with benign disease undergoing simple surgical procedures.	2
The rate of fistula formation following external beam radiotherapy for gynaecological cancer appears to be of the same order as that following surgical treatment.	4

4.8.2 ***Classification***

Due to the plethora of VVF classification systems, a consensual classification system needs to be adopted. The Waaldijk and Goh classifications are widely used for diagnosis and follow-up [688-690] but were originally designed for obstetric fistulae and their use in iatrogenic fistulae is less relevant [691]. Waaldijk's classification is based on the size and site of the fistulae and divides them into three main categories: type 1 are VVFs with no urethral involvement; type 2 are those that involve the urethra (and are sub-classified into those with circumferential and non-circumferential urethral involvement); and type 3 are fistulae involving other parts of the urinary tract. Goh's classification also uses the presence or absence of urethral involvement to sub-categorise VVFs and considers the degrees of fibrosis present. The WHO classification (Table 6) was originally developed for obstetric fistulae and separates fistulae into simple and complex.

Table 6: Adapted WHO Classification of fistulae [669]*

Simple fistula with good prognosis	Complex fistula with uncertain prognosis
• Single fistula < 4 cm • Vesico-vaginal fistula • Closing mechanism not involved • No circumferential defect • Minimal tissue loss • Ureters not involved • First attempt to repair	• Fistula > 4 cm • Multiple fistula • Recto-vaginal mixed fistula, cervical fistula • Closing mechanism involved • Scarring • Circumferential defect • Extensive tissue loss • Intravaginal ureters • Failed previous repair • Radiation fistula

**Although this classification was developed for obstetric fistula initially, it could be relevant for iatrogenic fistula as well.*

4.8.2.1 Recommendation for the classification of urinary fistula

Recommendation	Strength rating
Use a classification system for urinary tract fistulae to try to standardise terminology in this subject area.	Strong

4.8.3 ***Diagnostic evaluation***

Leakage of urine is the hallmark sign of a urogenital fistula. The leakage is usually painless, may be intermittent if it is position dependent, but more usually is constant. Unfortunately, intraoperative diagnosis of a genito-urinary or gastrointestinal injury is made in only about half of the cases [692]. Diagnosis of VVF usually requires clinical assessment often in combination with appropriate imaging or laboratory studies. As for any LUTS, history taking and focused physical examination with direct visual inspection are essential parts of urinary fistula diagnostic evaluation. Cystoscopy and retrograde bladder filling with a coloured fluid with placement of a tampon into the vagina to identify staining facilitate diagnosis of VVF. A double-dye test to differentiate between UVF and VVF may be useful in some cases [677]. Testing the creatinine level in either the extravasated or collected fluid will confirm fluid leakage as urine. Contrast-enhanced CT with late excretory phase reliably diagnoses urinary fistulae and provides information about ureteric integrity and the possible presence of associated urinoma. Magnetic resonance imaging, in particular with T2 weighting, also provides diagnostic information regarding fistulae [693].

Summary of evidence	LE
As for any LUTS, history taking and focused physical examination with direct visual inspection are essential parts of urinary fistula diagnostic evaluation.	3
Cystoscopy and retrograde bladder filling with a coloured fluid with placement of a tampon into the vagina to identify staining facilitate diagnosis of VVF.	3
Contrast-enhanced CT with late excretory phase reliably diagnoses urinary fistulae and provides information about ureteric integrity.	3
Magnetic resonance imaging, in particular with T2 weighting, also provides diagnostic information regarding fistulae.	3

Recommendations	Strength rating
Take a complete medical history and perform a focused physical examination including direct visual inspection for evaluation of women with suspicion of urinary fistula.	Strong
Use cystoscopy and retrograde bladder filling with a coloured fluid to confirm the diagnosis of urinary fistula.	Weak
Contrast-enhanced CT with late excretory phase and magnetic resonance imaging can be used in cases where the diagnosis of urinary fistula is challenging or to provide additional diagnostic information.	Weak

*4.8.4 **Management of fistula***

4.8.4.1 Management of vesico-vaginal fistula

4.8.4.1.1 Conservative management

4.8.4.1.1.1 Spontaneous closure

The reported spontaneous closure rate is 13 ± 23% [694], although this applies largely to small fistulae (< 1 cm) [668, 695]. Hence, immediate management is usually by urinary catheterisation or diversion; however, within the first two weeks following fistula occurrence, delayed surgical exploration and repair can be planned.

4.8.4.1.1.2 Pharmacotherapy

Several case reports describe a successful fistula closure rate following the induction of amenorrhoea by oestrogen, oestrogen/progesterone combinations or luteinising hormone releasing hormone analogues specifically for small (< 7 mm), uretero- or vesico-uterine fistulae following caesarean section [696-702]. One RCT comparing the efficacy of using fibrin glue compared to Martius flap inter-positioning (n = 14; < 4 cm and n = 5; > 5 cm) did not report significantly different outcomes between the two types of treatment but the closure rates were relatively low in both groups (68.4% vs. 57.9%) [703].

4.8.4.1.1.3 Palliation and skin care

During the intervening period between diagnosis and repair, UI pads with the aim of prevention of skin complications related to chronic urinary leakage can be provided and the use of a barrier cream or local oestrogen can also be considered [704, 705].

4.8.4.1.2 Surgical management

Overall closure rates after surgical repair of vesico-vaginal fistulae range from 58-100% [706].

4.8.4.1.2.1 Timing of surgery

Findings from small uncontrolled case series suggest no difference in success rates for early (within four weeks) or delayed (after three months) closure of VVF [707, 708].

4.8.4.1.2.2 Surgical approaches

Vaginal procedures

There are two main types of closure techniques applied to the repair of urinary fistulae, the classical saucerisation/partial colpocleisis [694] and the more commonly used dissection and repair in layers or flap-splitting technique [709]. There are no data comparing their outcomes.

Abdominal procedures

There are no RCTs comparing abdominal and vaginal approaches. Repair by the abdominal route is indicated when high fistulae are fixed at the vaginal vault and are inaccessible via a vaginal approach. A transvesical repair has the advantage of being entirely extraperitoneal. A simple transperitoneal repair is used less often

although it is favoured by some using the laparoscopic approach. A combined transperitoneal and transvesical procedure may be utilised for fistula repair following caesarean section. Results of secondary and subsequent repairs are not as successful as the initial repair [710].

Laparoscopic and robotic procedures
Small series (single figures) have reported using these techniques, but while laparoscopic repair is feasible with and without robotic assistance, no series to date have compared outcomes with alternative surgical approaches.

Trimming of fistula edge
A single RCT compared trimming of the fistula edge with no trimming. There was no difference in success rates but failed repairs in trimmed cases had larger recurrences than untrimmed cases, which were smaller [711].

Tissue interposition
Tissue flaps are often added as an additional layer of repair during VVF surgery. Most commonly, such flaps are utilised in the setting of recurrence after a prior attempt at repair, for VVF related to previous radiotherapy (described later), ischaemic or obstetric fistulae, large fistulae, and finally those associated with a difficult or tenuous closure due to poor tissue quality. However, there is no high-level evidence that the use of such flaps improves outcomes for either complicated or uncomplicated VVF.

Postoperative management
There is no high-level evidence to support any particular practice in postoperative management, but most reported series used catheter drainage for > 10 days and longer periods in complex or radiation-associated fistulae (up to three weeks). The performance of postoperative cystography prior to catheter removal can theoretically miss a persistent fistula if not done with a micturition phase or if the fistula is located at the bladder neck.

4.8.4.1.3 Management of complications of vesico-vaginal fistulae
The complications of VVF repair are varied and can include:
- Persistence or recurrence of fistula;
- Persistence or recurrence of UI;
- Persistence of LUTS or occurrence of new LUTS, including *de novo* OAB and/or SUI;
- Infections: wound and UTIs/urosepsis;
- Ureteric obstruction (ligation, fibrosis or injury);
- Bladder outlet obstruction (meatal stenosis, urethral stricture or bladder neck obstruction);
- Bladder contracture;
- Vaginal stenosis;
- Sexual dysfunction (vaginismus/dyspareunia);
- Rare complications (granulomas/diverticulum formation);
- Neurological complications (foot drop/neurogenic bladder);
- Psychological trauma (social isolation/divorce/mental illness);
- Infertility.

The literature on the treatment and management of complications of fistula repairs is scarce and is mostly experienced based. It is impossible to provide any specific evidence-based guidance.

4.8.4.2 Management of radiation fistulae
Modified surgical techniques are often required, and indeed, where the same techniques have been applied to both surgical and post-radiation fistulae, the results from the latter have been consistently poorer [712]. Due to the wide field abnormality surrounding many radiotherapy-associated fistulae, approaches include permanent urinary and/or faecal diversion [712, 713] or preliminary urinary and faecal diversion, with later undiversion in selected cases following reconstruction. In cases where life expectancy is deemed to be short, ureteric occlusion and nephrostomy insertion might be more appropriate.

4.8.4.3 Management of ureteric fistulae
Patients at higher risk of ureteric injury require experienced surgeons who can identify and protect the ureter and its blood supply to prevent injury and recognise injury promptly. Immediate repair of any intraoperative injury should be performed by observing the principles of debridement, adequate blood supply and tension-free anastomosis with internal drainage using stents [714]. Delayed presentation of UUT injury should be suspected in patients whose recovery after relevant abdominal or pelvic surgery is slower than expected, if there is any fluid leak, and if there is any unexpected dilatation of the pelvicalyceal system.

While there is no evidence to support the use of one surgical approach over another, there is consensus that repair should adhere to the standard principles of tissue repair and safe anastomosis and be undertaken by an experienced team. Conservative management is possible with internal or external drainage, endoluminal management using nephrostomy and stenting where available, and early (< 2 weeks) or delayed (> 3 months) surgical repair when required [715]. Functional and anatomical imaging should be used to follow-up patients after repair to guard against development of ureteric stricture and deterioration in renal function.

Uretero-vaginal fistula occurring in the early postoperative phase predominantly after hysterectomy is the most frequent presentation of UUT fistulae in urological practice. An RCT in 3,141 women undergoing open or laparoscopic gynaecological surgery found that prophylactic insertion of ureteric stents made no difference to the low risk (1%) of ureteric injury [716].

Endoscopic management is sometimes possible by retrograde stenting, percutaneous nephrostomy and antegrade stenting if there is pelvicalyceal dilatation, or ureteroscopic realignment [717]. However, the long-term success rate is unknown. Antegrade endoluminal distal ureteric occlusion combined with nephrostomy tube diversion often palliates urinary leakage due to malignant fistula in the terminal phase [718]. If endoluminal techniques fail or result in secondary stricture, the abdominal approach to repair is standard and may require end-to-end anastomosis, reimplantation into the bladder using psoas hitch or Boari flap, or replacement with bowel segments with or without reconfiguration. As a last resort, nephrectomy may be considered, particularly in the context of a poorly functioning kidney and an otherwise normal contralateral kidney [719-723].

4.8.4.3.1 Management of urethro-vaginal fistulae

4.8.4.3.1.1 Aetiology

Although urethro-vaginal fistulae are rare, most of them in adults have an iatrogenic aetiology. Causes include surgical treatment of SUI with bulking agents or synthetic slings, surgery for urethral diverticulum and genital reconstruction. Irradiation and even conservative treatment of prolapse with pessaries can lead to formation of fistulae.

4.8.4.3.1.2 Diagnostic evaluation

Clinical vaginal examination, including the three-swab test, is often sufficient to diagnose urethro-vaginal fistulae. Urethroscopy and cystoscopy can be performed to assess the extent and location of the fistulae. In cases of difficult diagnosis, VCUG or US can be useful. An 3D-MRI or CT scan is becoming utilised more widely to clarify anatomy [724, 725].

4.8.4.3.1.3 Surgical management

Choice of surgery will depend on the size, localisation, and aetiology of the fistula and the amount of tissue loss. Principles of reconstruction include identifying the fistula, creation of a plane between the vaginal wall and urethra, watertight closure of the urethral wall, eventual interposition of tissue, and closure of the vaginal wall.

One case series reported that a vaginal approach yielded a success rate of 70% at first attempt and 92% at second attempt, and that an abdominal approach only led to successful closure in 58% of cases [726]. A vaginal approach required less operating time, had less blood loss and shorter hospitalisation.

Most authors have described surgical principles that are identical to those of VVF repair, and primary closure rates of 53–95.4% have been described. A series of 71 women, treated for urethro-vaginal fistulae reported that 90.1% of fistulae were closed at the first vaginal intervention. Additionally, 7.4% were closed during a second vaginal intervention. Despite successful closure, SUI developed in 52% of cases. Stress urinary incontinence patients were treated with synthetic or autologous slings and nearly 60% became dry and an additional 32% improved. Urethral obstruction occurred in 5.6% and was managed by urethral dilation or urethrotomy [727].

4.8.4.3.1.4 Flaps and neo-urethra

The simplest flap is a vaginal advancement flap to cover the urethral suture line. Labial tissue can be harvested as a pedicled skin flap. This labial skin can be used as a patch to cover the urethral defect but can also be used to create a tubular neo-urethra [728, 729]. The construction of a neo-urethra has mostly been described in traumatic aetiologies. In some cases, a transpubic approach has been used [730]. The numbers of patients reported are small and there are no data on the long-term outcome of fistula closure and continence rates. The underlying bulbo-cavernosus tissue can be incorporated in the pedicled flap and probably offers better vascularisation and more bulking to the repair. This could allow a safer placement of a sling afterwards, in those cases where bothersome SUI would occur postoperatively [731, 732].

4.8.4.3.1.5 Martius flap

In obstetrical fistula repair, the Martius labial bulbocavernosus muscle/fat flap was not found to have any benefit. However, the Martius flap is still considered by some to be an important adjunctive measure in the treatment of genitourinary fistulae for which additional bulking with well-vascularised tissue is needed [733]. The series of non-obstetrical aetiology are small and all of them are retrospective. There are no prospective data, nor randomised studies [734]. The indications for Martius flap in the repair of urethra-vaginal fistulae remain unclear.

4.8.4.3.1.6 Rectus muscle flap

Rectus abdominis muscle flaps have been described by some authors [735, 736].

4.8.4.3.1.7 Alternative approaches

An alternative retropubic retro-urethral technique has been described by Koriatim [737]. This approach allows a urethro-vesical flap tube to be fashioned to form a continent neo-urethra.

4.8.4.4 Summary of evidence and recommendations for the management of urinary fistula

Summary of evidence	**LE**
Spontaneous closure of surgical fistulae does occur and appears more likely for small fistulae although it is not possible to establish the rate with any certainty.	3
There is no evidence that the timing of repair makes a difference to the chances of successful closure of a fistula.	3
There is no high-quality evidence of differing success rates for repair of VVFs by vaginal, abdominal, transvesical, and transperitoneal approaches.	3
A variety of interpositional grafts can be used in either abdominal or vaginal procedures, although there is little evidence to support their benefits in any specific setting.	3
Post-radiation fistula	
Success rates are lower for irradiated fistulae than for non-radiated fistulae.	3
Ureteric fistula	
Prophylactic ureteric stent insertion does not reduce risk of ureteric injury during gynaecological surgery.	2
Antegrade endoluminal distal ureteric occlusion combined with nephrostomy tube diversion often palliates urinary leakage due to malignant fistula in the terminal phase.	4
Urethro-vaginal fistula	
Urethro-vaginal fistula repair may be complicated by SUI, urethral stricture, and urethral shortening, which may necessitate long-term follow-up.	3

Recommendations	**Strength rating**
General	
When reporting on outcomes after fistula repair, authors should make a clear distinction between fistula closure rates and postoperative urinary incontinence rates and the time at which the follow-up was organised.	Strong
Do not routinely use ureteric stents as prophylaxis against injury during routine gynaecological surgery.	Strong
Suspect ureteric injury or fistula in patients following pelvic surgery if a fluid leak or pelvicalyceal dilatation occurs postoperatively, or if drainage fluid contains high levels of creatinine.	Strong
Use three-dimensional imaging techniques to diagnose and localise urinary fistulae, particularly in cases with negative direct visual inspection or cystoscopy.	Weak
Manage upper urinary tract fistulae initially by conservative or endoluminal techniques where such expertise and facilities exist.	Weak
Surgical principles	
Surgeons involved in fistula surgery should have appropriate training, skills, and experience to select an appropriate procedure for each patient.	Weak

Attention should be given as appropriate to skin care, nutrition, rehabilitation, counselling, and support prior to, and following, fistula repair.	Weak
Tailor the timing of fistula repair to the individual patient and surgeon requirements once any oedema, inflammation, tissue necrosis, or infection, are resolved.	Weak
Ensure that the bladder is continuously drained following fistula repair until healing is confirmed (expert opinion suggests: ten to fourteen days for simple and/or post-surgical fistulae; fourteen to 21 days for complex and/or post-radiation fistulae).	Weak
Where urinary and/or faecal diversions are required, avoid using irradiated tissue for repair.	Weak
Use interposition graft when repair of radiation associated fistulae is undertaken.	Weak
Repair persistent urogenital fistulas by an abdominal approach using open, laparoscopic, or robotic techniques according to availability and competence.	Weak
Urethro-vaginal fistulae should preferably be repaired by a vaginal approach.	Weak

4.9 Urethral diverticulum

A female urethral diverticulum is a sac-like protrusion composed of the entire urethral wall or only the urethral mucosa, situated between the peri-urethral tissues and the anterior vaginal wall.

*4.9.1 **Epidemiology, aetiology, pathophysiology***

Urethral diverticulum is an uncommon condition with an estimated prevalence of 1–6%. A prevalence of up to 10% was reported among women with LUTS attending a tertiary referral centre [738]. However, as many patients are asymptomatic or misdiagnosed, the true incidence is unknown [739-741]. Given the rarity of the condition, most published series are small and single institutional. Urethral diverticulum is thought to arise from repeated obstruction, infection, and subsequent rupture of peri-urethral glands into the urethral lumen, resulting in an epithelialised cavity that communicates with the urethra [739].

Iatrogenic damage to the urethra may also play a role, as up to 20% of women with urethral diverticula are noted to have a history of urethral surgery, dilation, or traumatic delivery [739, 742]. Iatrogenic urethral diverticula formation associated with synthetic sub-urethral sling has also been reported [743-745].

*4.9.2 **Classification***

Table 7: Classification system for female urethral diverticula based on characteristics*

Localisation	Mid-urethral Distal Proximal Full length
Configuration	Single Multi-loculated Saddle shaped
Communication	Mid-urethral No communication visualised Distal Proximal
Continence	Stress urinary incontinence Continent Post-void dribble Mixed incontinence

**Limited LNS C3 classification of urethral diverticula [742, 746, 747].*

*4.9.3 **Diagnostic evaluation***

The commonly encountered symptoms for urethral diverticulum such as pain, urgency, frequency, recurrent UTIs, vaginal discharge, dyspareunia, voiding difficulties or UI [748], are common to many other LUT dysfunctions. Consequently, there is no pathognomonic cluster of symptoms to identify urethral diverticulum. Many patients with urethral diverticulum are asymptomatic. However, urethral diverticulum often presents with a palpable urethral mass. It may be possible to express a purulent exudate from the urethra. Occasionally a stone may develop within the diverticulum.

Urethral diverticulum can be diagnosed by physical examination, VCUG and MRI. Other investigations include urethrocystoscopy, endocavitary (often transvaginal or sometimes transurethral) pelvic floor US and double balloon urethrography.

No robust diagnostic accuracy studies have addressed the question of the best test to confirm the diagnosis in women with clinical suspicion of urethral diverticulum. A case series of 27 patients concluded that endoluminal (vaginal or rectal) MRI has better diagnostic accuracy than VCUG [749] and determines the size and extent of urethral diverticulum more accurately. A case series of 60 patients reported that the sensitivity, specificity, positive predictive value and negative predictive value of MRI was 100%, 83%, 92% and 100%, respectively [750]. Another case series reported 100% specificity and sensitivity of MRI in 60 patients [751]. However, a case series of 41 patients reported a 25% discrepancy between MRI and surgical findings [752]. Endoluminal MRI with either a vaginal or rectal coil may provide even better image quality than simple MRI [753].

Magnetic resonance imaging is the gold standard for the diagnosis and planning of surgical repair and is also useful in diagnosing diverticular inflammation or tumour [754, 755].

Urethrocystoscopy can be used to visualise the ostia of the diverticula. Knowledge of the ostias' location and number can assist with surgical planning since they need to be closed after diverticulectomy. However, given the challenges of urethroscopy in women, the ostia are only seen in 42% of cases [748].

If VCUG is performed, antero-posterior and lateral images are required to optimally characterise the configuration of the diverticulum. There is a high risk of false negatives since the ostia of the diverticula must be patent and the patients must be able to void during the study. In more complex diverticula where there is septation, the entire diverticulum may not be visualised underestimating its complexity or size [756]. The sensitivity of VCUG is 73.5% which is significantly worse than MRI [748].

Ultrasound can be performed transabdominally, trans-vaginally or trans-perineally to identify the diverticulum. In particular, the transvaginal approach allows imaging of the urethra from the meatus to the bladder neck in several planes and can identify the number, size, location, and contents of the diverticulum. This technique is challenging and requires a skilled ultrasonographer. Additionally, the probe can compress the urethra, causing distortion [756]. A meta-analysis reported that US of any kind had a sensitivity of 82.0%, which was inferior to that of MRI [756]. However, a recent publication on trans-labial US reported a sensitivity of 95% [757]; therefore, this approach may be explored further by researchers in the future.

For patients who cannot undergo MRI and those in whom the ostia cannot be seen on cystoscopy, double balloon urethrography is an option. Sensitivity of 94.7% has been reported, which is comparable to that of MRI, but it is technically difficult, requires an experienced radiologist/radiographer and specialised equipment, can be painful for the patient and carries a risk of UTI. Given the current popularity of other imaging modalities, many units may not have access to this technique [756].

4.9.3.1 Associated voiding dysfunction

Although the presentation of urethral diverticulum is often non-specific and variable, urethral diverticulum can be associated with voiding dysfunction and SUI or UUI.

One recent series reported SUI in 60% of patients with urethral diverticulum [758]. Urethral diverticulum is most often located at the level of the mid-urethra. This location often overlaps with the external sphincter. However, urethral diverticulum may also extend proximally toward the bladder neck in the vicinity of the proximal sphincter mechanism. This morphology may, in part, explain the association between urethral diverticulum and SUI, with potentially more proximal lesions at risk for postoperative SUI [759].

Urethral diverticulum may also be associated with BOO due to the mass effect of the urethral diverticulum, urinary retention, or urgency and UUI [760]. Pain and dysuria associated with urethral diverticulum may also result in acquired voiding dysfunction.

Pressure–flow studies may have a role in the preoperative assessment of patients with urethral diverticula and coexisting voiding dysfunction or SUI [741, 761-763]. Indeed, urodynamics may evaluate coexisting detrusor dysfunction or document the presence of SUI or obstruction prior to repair [764, 765].

Urethral pressure profilometry has also been used in the assessment or diagnosis of urethral diverticulum, noting a biphasic pattern, or pressure drop at the level of the lesion [761, 763, 766]. Video-urodynamics may be helpful in differentiating SUI from paradoxical UI due to fluid accumulation in the urethral diverticulum. Additionally, resting and straining images obtained during fluoroscopic imaging may document an open bladder neck at rest. This may be a consideration in some patients with an extensive urethral diverticulum at the level of the mid-urethra, and potential implications for postoperative UI due to compromise of both sphincter mechanisms.

*4.9.4 **Disease management***

For women with minimal symptoms who would prefer to avoid invasive treatment, conservative management can be considered. Patients should be warned of the small risk of cancer (1–6%) within the diverticulum [767, 768].

4.9.4.1 Surgical treatment

No RCTs have investigated the effectiveness of surgery in women who have a bothersome urethral diverticulum. Thorough evaluation of the anatomy of the diverticulum is essential in planning reconstructive surgery.

There are three surgical approaches to treatment of diverticulum: marsupialisation, endoscopic incision, and curative treatment with diverticulectomy.

Surgical removal (diverticulectomy) is the most commonly reported treatment in contemporary case series. The principles of successful transvaginal diverticulectomy are to: dissect a well-vascularised vaginal flap; preserve the peri-urethral fascia for closure; remove all the diverticular wall; excise the ostium and close the urethra in a watertight fashion; close the incision in a multi-layered fashion with no overlapping suture lines; and preservation or creation of continence.

The decision to use a labial fat pad flap (commonly known as a Martius flap) varies, and the flap is used more frequently in the following situations: recurrent cases, large urethral defects or for deficient vaginal flaps for closure [742, 746] transection of the urethra required for access to a circumferential diverticulum [755] or in the case of complex configuration [760], and if there is a planned future sling procedure required for UI to facilitate the dissection at that time [742].

Marsupialisation involves incision into the mass on the vaginal side to drain the infected contents. The wall is sutured open with absorbable suture to allow drainage and prevent reaccumulating of infectious materials. This approach leaves the cystic structure in place and can theoretically cause a urethro-vaginal fistula because there is communication with the diverticular ostium, but it is a rapid procedure with little dissection required. This approach has been advocated in pregnant patients to decompress the diverticulum and allow safe vaginal delivery. A small case series suggested that 75% of pregnant women with urethral diverticula managed expectantly eventually required postpartum surgery [769].

Endoscopic incision is a rarely reported treatment option [770, 771]. This procedure involves finding the narrow neck of the ostium and incising it with a resectoscope. This unroofing of the diverticulum transforms the narrow communication with the urethra that causes symptoms when it becomes obstructed into a wide-mouthed sac that drains freely.

4.9.4.2 Management of concomitant stress urinary incontinence

Many women present with concomitant SUI and urethral diverticulum and may request both conditions to be simultaneously treated. A meta-analysis reported that diverticulectomy cured SUI even without a concomitant anti-incontinence procedure. However, no data regarding symptom severity were given and it could be assumed that many of these cured patients had less-severe UI before surgery [748]. Therefore, additional surgical correction may be required [759, 771]. However, there is no consensus on appropriate timing of surgical management of these two conditions. Thus, patients with symptomatic bothersome SUI in association with urethral diverticulum may be offered simultaneous anti-UI surgery. Although historical series have shown good

results with concomitant bladder neck suspension [765], more contemporary series have utilised pubovaginal fascial slings, with satisfactory outcomes [772-775]. Synthetic MUS are not recommended as a concomitant anti-UI procedure at the time of urethral diverticulectomy [776]. Synthetic material adjacent to a fresh suture line following diverticulectomy in the setting of potentially infected urine may place the patient at higher risk for subsequent urethral erosion and vaginal extrusion of the sling material, as well as urethro-vaginal fistula formation and foreign body granuloma formation.

4.9.4.3 Success rate and complications

Transvaginal urethral diverticulectomy has a high success rate (defined by being dry) of 84–98%, with a reoperation rate of 2–13% after primary repair during a mean follow-up of twelve to 50 months [739, 742, 759, 777]. The resolution of symptoms after surgery has been reported to reach 68.8% but less than half of studies comment on symptom improvement [778].

One case series reported a recurrence rate of 33% in U-shaped and of 60% in circumferential diverticula within one year [746], one study 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 [779] or radiation. Recurrent urethral diverticulum following initial successful urethral diverticulectomy may occur as a result of a new infection or traumatic insult such as childbirth, a new urethral diverticulum, or recurrence of the original lesion. Recurrence may be due to incomplete removal of the urethral diverticulum, inadequate closure of the urethra, residual dead space (circumferential diverticula), or other technical factors. Repeat urethral diverticulectomy represents a unique challenge due to altered anatomy, scarring, and difficulty identifying proper anatomical planes.

One case series reported that storage symptoms decreased significantly postoperatively from 60% to 16% following surgery for urethral diverticulum [759]. Other series with long-term follow-up, however, have demonstrated rates of postoperative urgency of 54% [779], and *de novo* UUI in 36% of patients [771]. Such postoperative symptoms indicate persistence of urethral diverticulum, recurrence of urethral diverticulum, or *de novo* OAB syndrome or urethral obstruction.

Stress urinary incontinence can be worsened or occur *de novo* after diverticulectomy. This is most likely due to sphincteric damage from the dissection or scarification preventing urethral closure. *De novo* SUI (10.6% of women) seems to be more common in proximal and large (> 30 mm) diverticula [759]. However, a retrospective review noted at least some *de novo* SUI in 49% of patients following urethral diverticulectomy; most of which was minor and did not require additional therapy [780]. Only 10% of these individuals underwent subsequent SUI surgery. Treatment for SUI after diverticulectomy is not well described in the literature. The most commonly reported operation is an autologous pubovaginal sling [770] followed by retropubic suspension [771]. However, there are two reported cases of synthetic mesh sling to treat SUI, without mesh complications [746, 759], but this is controversial.

Early common postoperative complications include UTI (0–39%), *de novo* SUI (3.8–33%), and *de novo* urinary retention (0–9%), especially in the setting of concomitant placement of an autologous pubovaginal sling [739, 742, 759, 777]. Delayed complications such as urethral stricture are reported in 0–5.2% of cases [739, 742, 771, 777]. Urethro-vaginal fistula is a devastating complication presenting in 0.9–8.3% of cases [781]. A distal fistula located beyond the sphincteric mechanism can present with split urinary stream or vaginal voiding and may not require repair. However, a fistula located anywhere from the mid-urethra to the bladder neck may result in UI. These patients should undergo repair with consideration of an adjuvant tissue flap, such as a Martius flap, to aid in closure. The timing of the fistula repair is not well defined, with a delay of three to six months after the initial repair being a good balance between patient discomfort and optimal tissue quality. Rare complications include: distal urethral necrosis, bladder injury, urethral injury, ureteric injury, and vaginal scarring or narrowing with consequent dyspareunia [781].

4.9.4.4 Pathological findings

Most urethral diverticula are lined with squamous cells, urothelium or columnar epithelium [742, 782, 783]. In a meta-analysis, there was a high prevalence of chronic or acute inflammation (68.6%) and the most commonly reported lesions were nephrogenic metaplasia, which occurred in 8% of cases. Diverticula may undergo neoplastic alterations (6%), including invasive adenocarcinoma [784], followed by squamous cell carcinoma in 0.7%. It is unknown if the diverticulum forms first and then transforms into a malignancy or if the malignancy develops first. These malignancies are treated in a similar fashion to urethral cancer in women.

4.9.5 *Summary of evidence and recommendations for urethral diverticulum*

Summary of evidence	LE
Magnetic resonance imaging has the best sensitivity and specificity for the diagnosis of urethral diverticulum.	3
Surgical removal of symptomatic urethral diverticulum provides good long-term results; however, women should be counselled of the risk of recurrence and *de novo* SUI.	3

Recommendations	Strength rating
Use magnetic resonance imaging for diagnosis and characterisation of urethral diverticula, with urethroscopy, voiding cystourethrogram and ultrasound where necessary.	Weak
Offer surgical removal of symptomatic urethral diverticulum.	Weak
If conservative treatment is adopted, warn patients of the small (1–6%) risk of cancer developing within the diverticulum.	Weak
Carefully question and investigate patients for coexisting voiding dysfunction and urinary incontinence (UI).	Strong
Following appropriate counselling, address bothersome stress urinary incontinence at the time of urethral diverticulectomy with concomitant non-synthetic sling.	Weak
Counsel patients regarding the possibility of *de novo* or persistent LUTS including UI, despite technically successful urethral diverticulectomy.	Strong

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6. CONFLICT OF INTEREST

All members of the Non-neurogenic Female LUTS Panel have provided disclosure statements of all relationships that they have that might be perceived as a potential source of a conflict of interest. This information is publically accessible through the European Association of Urology website: https://uroweb.org/guideline/non-neurogenic-female-luts/.

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.

7. CITATION INFORMATION

The format in which to cite the EAU Guidelines will vary depending on the style guide of the journal in which the citation appears. Accordingly, the number of authors or whether, for instance, to include the publisher, location, or an ISBN number may vary.

The compilation of the complete Guidelines should be referenced as:
EAU Guidelines. Edn. presented at the EAU Annual Congress Paris 2024. ISBN 978-94-92671-23-3.

If a publisher and/or location is required, include:
EAU Guidelines Office, Arnhem, The Netherlands. http://uroweb.org/guidelines/compilations-of-all-guidelines/

References to individual guidelines should be structured in the following way:
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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 pelvic pain and associated lower abdominal pain. From both literature and daily practice it has become clear that lower 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 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 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 whilist taking personal values and preferences/individual circumstances of patients into account through shared decision-making. Guidelines are not mandates and do not purport to be a legal standard of care.

Structure and scope

The panel wishes to take advantage of modern methods of delivering guideline information to clinicians dealing with these patients. In 2016, a stepped information structure was made, in alignment with stepped care protocols, using new digital information sources like websites and apps to aid this process. Furthermore, the guideline was changed according to the template used in all other non-oncology guidelines of the EAU. It was recognised that structuring a guideline on chronic pain is quite different from structuring one on another subject. A multi-disciplinary approach is of utmost importance and demands a broad view. In 2016, the guideline was rewritten to be centred around pain instead of being organ-centred. It is partly theoretical to show the importance of using this pain-centred approach. The biggest part, however, deals with the practical approach to diagnostics, treatment and management of patients with abdominal and pelvic pain.

1.2 Publication history

The EAU Guidelines on Chronic Pelvic Pain were first published in 2003 [1] which formed the basis of a scientific publication in European Urology in 2004 [2]. Also, in the 2003 edition the concept of Chronic Pelvic Pain Syndromes (CPPS) was introduced, which is now referred to as “pain as a disease process”. Partial updates of the Chronic Pelvic Pain 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 Chapter 5 ‘Gastrointestinal aspects of chronic pelvic pain’ and Chapter 8 ‘Psychological aspects of chronic pelvic pain’. The next update of the Chronic Pelvic Pain Guidelines will be published in 2024.

For the 2015 edition the panel critically reviewed the sub-chapter on chronic primary bladder pain syndrome (BPS) which is now a comprehensive part of the guideline. The fact that this part was so extensive shows that the roots of talking about abdominal pain and pelvic pain lies in the bladder, where Interstitial Cystitis was one of the first subjects addressed talking about pain in urology. The panel has illustrated this in the publication in European Urology in 2013 [5].

1.3 Available Publications

Alongside the full text version, a quick reference document (Pocket Guidelines) is available in print. This is an abridged version which may require consultation together with the full text version. This reference document follows the updating cycle of the underlying large texts. All available material can be viewed at the EAU website. The EAU website also includes a selection of EAU Guideline articles as well as translations produced by national urological associations: https://uroweb.org/guidelines/chronic-pelvic-pain

1.4 Panel composition

The panel of experts responsible for this guideline include five urologists, (one of whom has a subspecialisation in neuro-urology and one is a sexologist), three consultants in pain medicine, a uro-gynaecologist, a psychologist, a gastroenterologist, a pelvic physiotherapist, health scientist and (clinical) epidemiologist and two patient advocates.

1.5 Terminology

Definitions of chronic pelvic pain terminology

Classification

Much debate over the classification of chronic pelvic pain 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 lesions and glomerulations on cystoscopy, whereas other bladder pain conditions may have a normal appearance on cystoscopy. These are two different phenotypes. The same is true for irritable bowel syndrome (IBS), which may be sub-divided into that associated primarily with diarrhoea or that with constipation. Phenotyping is based upon mechanisms when they are known (e.g., infection, ischaemic, auto-immune, 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. The World Health Organization (WHO) International Classification of Diseases 11th Revision (ICD-11) uses the term Chronic Primary Pain to distinguish these conditions from pain associated with another diagnosis that they refer to as Chronic Secondary Pain (see below).

Terminology

Terminology is the word(s) 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 BPS. The EAU, the International Society for the study of BPS (known as ESSIC), the International Association for the Study of Pain (IASP) and several other groups have preferred the term BPS. 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" should particularly be avoided, unless infection and or inflammation is proven and considered to be the cause of the pain [6]. It must be appreciated that end-organ inflammation may be secondary and neurogenic in origin and not a primary cause of the pain.

Taxonomy

Taxonomy places the phenotypes into a relationship hierarchy. The EAU approach sub-divides chronic pelvic pain into conditions that are pain syndromes with no obvious diagnosis, chronic primary pelvic pain syndromes (CPPPS) (consistent with ICD-11 Chronic Primary Pain) 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 nonpain syndromes include "classical conditions", "well-defined conditions" and "confusable diseases" and the ICD-11 Chronic Secondary Pain. 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 chronic pelvic pain

Importance of classification

It should be obvious to all that a condition cannot be treated unless it is defined. However, the reasons for classifying chronic pelvic pain go far beyond that.

Clues to the mechanism

As a result of systematic phenotypic and taxonomic classifications, similarities and differences between conditions become clear. Drawing comparisons between the phenotypes of different disorders allows comparison between disorders such as bladder and bowel pain syndromes, thus facilitating research and treatment.

Guidelines for best treatment options
As conditions become better defined, more specific treatment approaches can be adopted. In particular, there will be a move away from treatments based upon spurious terms (e.g., antibiotics and non-steroidal anti-inflammatory drugs for the "-itis" conditions). Generic treatments aimed at groups of conditions will be more commonplace and based upon research evidence.

Research platform
Only by clearly defining the phenotype being investigated can research be valued or applied to the clinical situation.

Patient needs
A diagnosis, or name, for a set of symptoms can provide patients with a sense of being understood, as well as hope for relief. It may 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 assist in self-management. However, it may lead to the accessing of information of variable quality associated with the diagnosis or name, and the possibility of generating new concerns about long-term consequences or about the appropriateness of treatment.

IASP definitions
Sub-dividing pain syndromes
There is much debate on the sub-divisions of the pain syndromes within the hierarchical taxonomy. The EAU has led the way in this regard and the guiding principles are as follows [2]:

1. The pain syndromes are defined by a process of exclusion. In particular, there should be no evidence of infection or inflammation. Investigations by end-organ specialists should therefore be aimed at obtaining a differential diagnosis; repeated, unnecessary investigations are detrimental in the management of chronic pain syndromes.
2. A sub-division phenotype should only be used if there is adequate evidence to support its use. For instance, in non-specific, poorly localised pelvic pain without obvious pathology, only the term chronic primary pelvic pain syndrome (CPPPS) 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, also potentially with the term primary added. If the pain is localised to multiple organs, then the syndrome is a regional pain syndrome and the term CPPPS 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. A North American research program, 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 the panel introduced the concept of managing the polysymptomatic nature of CPPPS, since then others have developed their own schemes, such as Nickel's UPOINT [7], modified by Magri *et al.* with the addition of a sexual dysfunction domain [8]. In light of these and other publications, the symptom classification table has been updated (Table 1).

The debate in relation to sub-dividing the pain syndromes continues. As more information is collected suggesting that the central nervous system (CNS) is involved, and indeed may be the main cause of many CPPPS conditions (e.g., bladder, genitalia, colorectal or myofascial), therefore there is a general tendency to move away from end-organ nomenclature. Only time and good research will determine whether this is appropriate. To enable such research, it is essential to have a framework of classification within which to work. Any hierarchical taxonomy must be flexible to allow change.

ICD classification: purpose and uses
The International Classification of Diseases is the foundation for the identification of health trends and statistics globally, and the international standard for reporting diseases and health conditions. It is the diagnostic classification standard for all clinical and research purposes. It defines the universe of diseases, disorders, injuries and other related health conditions, listed in a comprehensive and hierarchical fashion [9]. The latest version, ICD-11, is available for member states to report with from January 2022.

The ICD-11 classification for the first time included chronic pain ("chronic pain is pain that persists or recurs for longer than three months") and divided the coding into Chronic Primary Pain ("chronic primary pain is multi-factorial: biological, psychological and social factors contribute to the pain syndrome") and a number of Chronic Secondary Pain conditions (related to cancer, post surgical, musculoskeletal, visceral, neuropathic, headache/ orofacial, other).

The significance of the inclusion of Chronic Pain as a condition within the ICD-11 should not be underestimated. There are, however, unresolved issues regarding this classification, such as when a condition ends and pain persists, does the term Chronic Secondary Pain become Chronic Primary Pain? [10, 11]. Similarly, the contents of recent drafted National Institute for Health and Care excellence (NICE) guidelines [12] (https://www.nice.org.uk/guidance/GID-NG10069/documents/draft-guideline), were found to be contentious as the guideline considered all Chronic Primary Pain as being essentially the same and the 'biological' nature of the pain appeared to have been missed. Whereas in the final guidelines this may be corrected, it does illustrate the risk behind the term Chronic Primary Pain.

The panel have changed the EAU terminology previously used in the Guidelines to show conformity with ICD 11 definitions. This will include changing terminology used in originally cited works.

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The classification has been set up according to the axis system used by IASP.

Table 1: EAU Classification of Chronic Pelvic Pain Syndromes

Axis I Region	Axis II System	Axis III End-organ as pain syndrome as identified from Hx, Ex and Ix	Axis IV Referral characteristics	Axis V Temporal characteristics	Axis VI Character	Axis VII Associated symptoms	Axis VIII Psychological symptoms
Chronic pelvic pain	Urological	Prostate	Suprapubic Inguinal Urethral Penile/clitoral Perineal Rectal Back Buttocks Thighs	ONSET Acute Chronic ONGOING Sporadic Cyclical Continuous TIME Filling Emptying Immediate post Late post TRIGGER Provoked Spontaneous	Aching Burning Stabbing Electric	UROLOGICAL Frequency Nocturia Hesitancy Dysfunctional flow Urgency Incontinence GYNAECOLOGICAL Menstrual Menopause GASTROINTESTINAL Constipation Diarrhoea Bloatedness Urgency Incontinence NEUROLOGICAL Dysaesthesia Hyperaesthesia Allodynia Hyperalgesia SEXUOLOGICAL Satisfaction Female dyspareunia Sexual avoidance Erectile dysfunction Medication MUSCLE Function impairment Fasciculation CUTANEOUS Trophic changes Sensory changes	ANXIETY About pain or putative cause of pain Catastrophic thinking about Pain DEPRESSION Attributed to pain or impact of pain Attributed to other causes Unattributed PTSD SYMPTOMS Re-experiencing Avoidance
		Bladder					
		Scrotal Testicular Epididymal					
		Penile Urethral					
		Post-vasectomy					
	Gynaecological	Vulvar Vestibular Clitoral					
		Endometriosis associated					
		CPPPS with cyclical exacerbations					
		Dysmenorrhoea					
	Gastrointestinal	Irritable bowel					
		Chronic anal					
		Intermittent chronic anal					
	Peripheral nerves	Pudendal pain syndrome					
	Sexological	Dyspareunia					
		Pelvic pain with sexual dysfunction					
	Psychological	Any pelvic organ					
	Musculo-skeletal	Pelvic floor muscle Abdominal muscle Spinal					
		Coccyx Hip muscle					
Chronic secondary pelvic pain syndrome, formally known as specific disease associated pelvic pain OR Chronic primary pelvic pain syndrome, formally known as pelvic pain syndrome							

Hx = History; Ex = Examination; Ix = Investigation; PTSD = post-traumatic stress disorder.

Pain syndromes
The original EAU classification [2] was inspired by the IASP classification [13] and much work around what has become known as "pain as a disease" and its associated psychological, behavioural, sexual, social and organ function aspects. After ten years of work developing the initial ideas, an updated version was accepted by the IASP Council for publication in January 2012.

EAU Definition of chronic pelvic pain
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 (LUT), 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) have localised the pain as being discerned in a specified anatomical pelvic area.]

In the case of documented nociceptive pain that becomes chronic/persistent through time, pain must have been continuous or recurrent for at least three months (in accordance with ICD-11). For cyclical pain, a longer period of more than six months may be appropriate. Cyclical pain is included in the classification, particularly if there is evidence of central sensitisation and hence dysmenorrhoea (hormonally dependent) needs to be considered as a chronic pain syndrome, if it is persistent and associated with negative cognitive, behavioural, sexual, or emotional consequences.

Chronic pelvic pain may be sub-divided into conditions with well-defined classical pathology (such as infection or cancer) and those with no obvious pathology but still including biological mechanisms. For the purpose of the EAU's classification, the term "specific disease-associated pelvic pain" has been accepted for the former, and "chronic pelvic pain syndrome" for the latter. In the new ICD-11 these conditions have new names: the former will be called Chronic Secondary Pelvic Pain and the latter Chronic Primary Pelvic Pain.

The following classification only deals with Chronic Primary Pelvic Pain Syndromes.

EAU Definition of chronic primary pelvic pain syndrome
Chronic primary pelvic pain syndrome (CPPPS) is the occurrence of chronic pain 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 LUT, sexual, bowel or gynaecological dysfunction. Chronic Primary Pelvic Pain Syndrome is a subdivision of chronic pelvic pain. Throughout the text below in the 2021 update, CPPS is replaced with CPPPS if it is appropriate.

Further subdivision of chronic primary pelvic pain syndrome
within a single organ, more than one pelvic organ and even associated with systemic symptoms such as chronic fatigue syndrome (CFS), fibromyalgia (FM) or Sjögren's syndrome. When the pain is localised to a single organ, some specialists may wish to consider using an end organ term such as BPS (Table 2), also using the term primary. 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 generic term CPPPS should be used. Many, including some of the panel members never sub-divide by anatomy and prefer to refer to patients with pain perceived within the pelvis, and no specific disease process, as suffering from CPPPS, sub-divided by psychological and functional symptoms.

Psychological considerations for classification
Many CPPPSs 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. 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 CPPPS. In all patients with CPPPS, 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) [14].

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 therefore bowel control is altered. The term is not used in the sense of a psychiatric functional disorder. Many CPPPSs 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 include significant pathology in the organs that appear responsible for the primary symptoms, but they are associated with substantial neurobiological, physiological and sometimes anatomical changes in the CNS.

Multi-system sub-division

It is recognised that the end-organ where the pain is perceived may not be the centre of pain generation. This classification is based upon the most effective and accepted method of classifying and identifying different pain syndromes, that is, by site of presentation. It is argued that keeping the end-organ name in the classification is inappropriate because, in most cases, there are multi-systemic causes and effects, with the result that symptoms are perceived in several areas. This is an area in which discussions are ongoing, and despite there being strong arguments for both keeping and dispensing with end-organ classification, the panel have not taken the umbrella approach of referring to all pain perceived in the pelvis as CPPS, primary or secondary.

Dyspareunia

Dyspareunia is defined as pain perceived within the pelvis associated with penetrative sex. It tells us nothing about the mechanism and may be applied to women and men. It is usually applied to penile penetration, but is often associated with pain during insertion of any object. It may apply to anal as well as vaginal intercourse. It is classically sub-divided into superficial and deep.

Primary perineal pain syndrome

Primary 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 LUT, sexual, bowel or gynaecological dysfunction. Primary perineal pain syndrome should be distinguished from pudendal neuralgia which is a specific disease associated with perineal pain that is caused by nerve damage.

Table 2: Chronic Primary Pelvic Pain Syndromes (the term primary can be included in any of the following)

Urological Pain Syndromes	
Primary prostate pain syndrome	Primary prostate pain syndrome (PPPS) 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. Primary prostate 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. The term “chronic prostatitis” continues to be equated with that of PPPS. 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 [15] includes infection (types I and II), which the authors feel should not be considered under PPPS, 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 CPPPS of the male is used instead of PPPS, which has been agreed by the majority.

Primary bladder pain syndrome	Primary bladder pain syndrome 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. Primary bladder 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. PBPS is believed to represent a heterogeneous spectrum of disorders. There may be specific types of inflammation as a feature in subsets of patients. Localisation of the pain can be difficult by examination, and consequently, another localising symptom is required. Cystoscopy with hydrodistension and biopsy may be indicated to define phenotypes. Recently, ESSIC has suggested a standardised scheme of sub-classifications [16] 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.
Primary scrotal pain syndrome	Primary scrotal pain syndrome is the occurrence of persistent or recurrent episodic pain localised to the scrotum or the structure within it and may be associated with symptoms suggestive of lower urinary tract or sexual dysfunction. There is no proven infection or other obvious local pathology. Primary scrotal pain syndrome is often associated with negative cognitive, behavioural, sexual or emotional consequences. Primary 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.
Primary testicular pain syndrome	Primary testicular pain syndrome is the occurrence of persistent or recurrent episodic pain perceived in the testes, and may be associated with symptoms suggestive of lower urinary tract or sexual dysfunction. There is no proven infection or other obvious local pathology. Primary testicular pain syndrome is often associated with negative cognitive, behavioural, sexual or emotional consequences. Previous terms have included orchitis, orchialgia and orchiodynia. These terms are no longer recommended.
Primary epididymal pain syndrome	Primary epididymal pain syndrome is the occurrence of persistent or recurrent episodic pain perceived in the epididymis, and may be associated with symptoms suggestive of lower urinary tract or sexual dysfunction. There is no proven infection or other obvious local pathology. Primary epididymal pain syndrome is often associated with negative cognitive, behavioural, sexual or emotional consequences.
Primary penile pain syndrome	Primary 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. Primary 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.
Primary urethral pain syndrome	Primary 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. Primary 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. Primary 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. The mechanisms are poorly understood and for that reason it is considered by some a special form of primary scrotal pain syndrome.

Primary Gynaecological Pain Syndromes: external genitalia	
Primary vulvar pain syndrome	Primary 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 primary vulvar pain syndrome. According to the ISSVD, vulvodynia is vulvar pain that is not accounted for by any physical findings. The ISSVD has defined vulvodynia as "vulvar discomfort, most often described as burning pain, occurring in the absence of relevant visible findings or a specific, clinically identifiable, neurologic disorder". If physical findings are present, the patient is said to have vulvar pain due to a specified cause. The ISSVD has sub-divided vulvodynia based on pain location and temporal characteristics of the pain (e.g. provoked or unprovoked). The following definitions are based on that approach.
Primary generalised vulvar pain syndrome	Primary 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 these are no longer recommended.
Primary localised vulvar pain syndrome	Primary 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). Primary localised vulvar pain syndrome can be sub-divided into primary vestibular pain syndrome and primary clitoral pain syndrome.
Primary vestibular pain syndrome	Primary 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.
Primary clitoral pain syndrome	Primary 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 primary pelvic pain syndrome with cyclical exacerbations	Chronic primary pelvic pain syndrome with cyclical exacerbations covers the non-gynaecological organ pain that frequently shows cyclical exacerbations (e.g., IBS or PBPS) 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.

Primary dysmenorrhoea	Primary dysmenorrhoea is pain with menstruation that is not associated with well-defined pathology. Dysmenorrhoea needs to be considered as a chronic primary pain syndrome if it is persistent and associated with negative cognitive, behavioural, sexual or emotional consequences.
Gastrointestinal Pelvic Pain Syndromes	
Irritable bowel syndrome	Irritable bowel syndrome is the occurrence of chronic or recurrent episodic (abdominal) pain associated with defecation or change in bowel habits. In routine diagnostic examination, obvious anatomic or physiologic abnormalities are absent. Bowel dysfunction (e.g. constipation) is frequent. Irritable bowel syndrome is often associated with worry and pre-occupation about bowel function, and negative cognitive, behavioural, sexual or emotional consequences, as well as with symptoms suggestive of lower urinary tract or gynaecological dysfunction. The classification is based upon the Rome IV Criteria [17]. Reccurent abdominal pain on average at least 1d/week in the last 3 months. Symptom onset at least 6 months prior to diagnosis. The pain is associated with at least two or more of the following criteria: Related to defecation, assocated with a change in frequency of stool or a change in form of stool. Depending on the predominant stool form, based on the Bristol Stool Scale, the IBS can be subdivieded into IBS with predominant constiation (IBS-C), predominant diarrhea (IBS-D) and with mixed bowel habits (IBS-M). Patients whose bowel habits don't fit in one of the above categories are classified as «IBS Unclassified» (IBS-U). Extra-intestinal symptoms include: nausea, fatigue, full sensation after even a small meal, and vomiting.
Chronic primary anal pain syndrome	Chronic primary 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 primary 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 primary anal pain syndrome	Intermittent chronic primary anal pain syndrome refers to severe, brief, episodic pain that seems to arise in the rectum or anal canal and occurs at irregular intervals. This is unrelated to the need to or the process of defecation. It may be considered a sub-group of the chronic primary anal pain syndromes. It was previously known as "proctalgia fugax" but this term is no longer recommended.
Musculoskeletal System	
Primary pelvic floor muscle pain syndrome	Primary pelvic floor muscle pain syndrome is the occurrence of persistent or recurrent episodic pelvic floor pain. There is no proven well-defined local pathology. It is often associated with negative cognitive, behavioural, sexual or emotional consequences, as well as with symptoms suggestive of lower urinary tract, sexual, bowel or gynaecological dysfunction. This syndrome may be associated with over-activity of, or trigger points within, the pelvic floor muscles. Trigger points may also be found in several muscles, such as the abdominal, thigh and paraspinal muscles and even those not directly related to the pelvis.
Primary coccyx pain syndrome	Primary 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. Primary 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.
Chronic Pain Post-Surgery	
Chronic post-surgical pain syndrome	The definition of chronic post-surgical pain is chronic pain that develops or increases in intensity after a surgical procedure and persists beyond the healing process, i.e., at least three months after the surgery. There is a separate category for this in the ICD11 classification.

2. METHODOLOGY

2.1 Methods

Additional information can be found in the general Methodology section online at the EAU website: https://uroweb.org/guidelines. A list of associations endorsing the EAU Guidelines can also be viewed online at the above address.

Recommendations within the Guidelines are developed by the panels to prioritise clinically important care decisions. The strength of each recommendation is determined by the balance between desirable and undesirable consequences of alternative management strategies, the quality of the evidence (including certainty of estimates), and the nature and variability of patient values and preferences. This decision process, which can be reviewed in the strength rating forms which accompany each guideline statement, addresses a number of key elements:

1. the overall quality of the evidence which exists for the recommendation [18];
2. the magnitude of the effect (individual or combined effects);
3. the certainty of the results (precision, consistency, heterogeneity and other statistical or study related factors);
4. 4the balance between desirable and undesirable outcomes;
5. the impact and certainty of patient values and preferences on the intervention.

Strong recommendations typically indicate a high degree of evidence quality and / or a favourable balance of benefit to harm and patient preference. Weak recommendations typically indicate availability of lower quality evidence, and/or equivocal balance between benefit and harm, and uncertainty or variability of patient preference [19].

The 2012 full text update was based on a systematic review (SR) 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. Where no LE: 1 literature could be identified the search was moved down to the next lower level on the rating scale.

Extensive use of free text ensured the sensitivity of the searches, resulting in a substantial body of literature to scan. Searches covered the period January 1995 to July 2011 and were restricted to English language publications. In 2017, a scoping search for the previous five years was performed and the guideline was updated accordingly.

In 2021, a new section was included on Post-Surgical Pain Syndrome. In addition, the classifications in the Guideline have been amended to reflect ICD-11 released by WHO. The latest version of ICD-11 will be available for member states to report with from January 2022. For the 2024 print, a scoping search for the previous three years was performed and the guideline was updated accordingly.

2.2 Review

This document was subject to peer review prior to publication in 2021.

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, or resembling that associated with, actual or potential tissue damage (IASP Taxonomy) [20].

Introduction to chronic pelvic primary pain syndromes

Over the years much of the focus for chronic pelvic primary pain syndromes (CPPPSs) 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 CPPPSs are based within the CNS. Although a peripheral stimulus such as infection may initiate the start of a CPPPS 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 form the basis of the pain syndrome diagnosis and each individual phenomenon needs to be addressed in its own right through multispecialty and multi-disciplinary care. Although ongoing peripheral organ pathology can produce persistent and chronic pain, the main focus of these guidelines is on CPPPSs 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***

Across the world [21] chronic pain is prevalent, seriously affecting the quality of people's social, family, and working lives, with differences between countries attributable to multiple causes, including study methodology. A UK study found a prevalence of chronic pelvic pain of 14.8% in women 25 years [22, 23].

*3.1.3 **Influence on Quality of Life***

Assessing QoL in pelvic pain patients is challenging due to the complex pathology, the multi-faceted nature of the complaints and the overlap between the different pelvic pain syndromes.

Pelvic pain syndromes have an impact in terms of QoL [24, 25], depression, anxiety, impaired emotional functioning, insomnia and fatigue [24, 26]. If these aspects are identified and targeted early in the diagnostic process, the associated pain symptoms may also improve. Addressing comorbidities will help in further improving QoL. Quality of life assessment is therefore important in patients with pelvic pain and should include physical, psychosocial behavioural and emotional aspects, using standardised instruments where possible. Chronic pain is, in many countries, the leading cause of years lost to disability [21], although these figures are dominated by musculoskeletal pain and headache. Chronic pain is often associated with depression and other psychological problems; with loss or reduction of work and of ability to carry out domestic tasks; and, with substantial use of healthcare, often with disappointing outcomes.

*3.1.4 **Costs***

No adequate data on costs were found.

*3.1.5 **Risk Factors and underlying causes***

3.1.5.1 Risk factors

Risk factors include many different factors from various areas, including genetic, psychological state, recurrent physical trauma and endocrine factors.

The endocrine system is involved in visceral function. Significant life events, and in particular, early life events may alter the development of the hypothalamic-pituitary-adrenal axis and the chemicals released. Increased vulnerability to stress is thought to be partly due to increased corticotrophin-releasing hormone (CRH) gene expression. Up-regulation of CRH has been implicated in several pain states such as rectal hypersensitivity to rectal distension [27]. This model suggests an action of CRH on mast cells. A range of stress-related illnesses have been suggested, e.g., IBS and BPS [28, 29]. There is evidence accumulating to suggest that the sex hormones also modulate both nociception and pain perception [30]. 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 [31]. Asking the patient about these events is important as they have an effect on a patient's psychological wellbeing [32, 33].

Genetics also play a role in assessing the risk of developing chronic pain. An individual who has one chronic pain syndrome is more likely to develop another. Family clusters of pain conditions are also observed and animals can be bred to be more prone to apparent chronic pain state. A range of genetic variations have been described that may explain the pain in certain cases; many of these are to do with subtle changes in transmitters and their receptors. However, the picture is more complicated in that developmental, environmental and social factors also influence the situation. Evidence that primary bladder pain syndrome (PBPS) may have

a genetic component has been presented in several identical twin studies, but genetics may contribute to less than one third of total variation in susceptibility to PBPS [34, 35].

Studies about integrating the psychological factors of CPPPSs are few but the quality is high. Psychological factors are consistently found to be relevant in the maintenance of persistent pelvic and urogenital pain [36]. Beliefs about pain contribute to the experience of pain [37] and symptom-related anxiety and central pain amplification may be measurably linked, and worrying about pain and perceived stress predict worsening of urological chronic pain over a year [36, 38]. Central sensitisation has been demonstrated in a small study of symptomatic endometriosis [39] and central changes are evident in association with dysmenorrhoea and increasingly recognised as a risk for female pelvic pain [40]. The various mechanisms of CNS facilitation, amplification and failure of inhibition mean that there is no simple relationship between physical findings, pain experience and resulting distress and restriction of activities. Division of aetiology into organic vs. psychogenic is unscientific. Diagnoses that assign women's pain to psychological origins due to scepticism about the reality or severity of their pain [23, 41] undermines any therapeutic relationship [42]. Pelvic pain and distress is related [43] in both men and women [44]; as are painful bladder and distress [38]. In a large population based study of men, CPPPS was associated with prior anxiety disorder [45]. The only SR [46] of risk factors for chronic non-cyclical pelvic pain in women included, as well as medical variables: sexual or physical abuse (Odds Ratio (OR): 1.51-3.49); psychological problems such as anxiety (OR: 2.28; 95% Confidence Interval (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 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 [47]. It is hard to establish a causal role for sexual abuse or trauma history, anxiety or depression in women with CPPPS [48, 49], as the attribution of current pain to past sexual or physical abuse is associated both with current depression [50] and with current overall physical health [51]. There is some evidence for a specific relationship between rape and CPPPS (and with fibromyalgia and functional gastrointestinal disorders) [52]; and, recent sexual assault may prompt presentation of pelvic pain [47, 53]. 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 [52], but men who reported having experienced sexual, physical or emotional abuse had increased odds (3.3 vs. 1.7) for symptoms suggestive of CPPPS [54]. Both sexes should be screened for sexual abuse when presenting with symptoms suggestive of CPPPS, and clinicians should inquire about pelvic pain in patients who have experienced abuse [54].

3.1.5.2 Underlying causes

The mechanisms that serve as an underlying cause for chronic pelvic pain are:

1. Ongoing acute pain mechanisms [55] (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 [56, 57]

Symptoms and signs of neuropathic pain appear to be common in CPPPS patients and assessment of neuropathic pain should be considered in that group of patients including those with secondary pelvic pain and other pelvic pathologies [58].

Chronic pain mechanisms may include altered resting state neuromotor connectivity, for instance in men with chronic prostatitis/CPPPS [59].

Table 3 illustrates some of the differences between the somatic and visceral pain mechanisms. These underlie some of the mechanisms that may produce the classical features of visceral pain; in particular, referred pain and hyperalgesia.

Table 3: Comparison between visceral and somatic pain

	Visceral pain	Somatic pain
Effective painful stimuli	Stretching and distension, producing poorly localised pain.	Mechanical, thermal, chemical and electrical stimuli, producing well localised pain.
Summation	Widespread stimulation produces significantly magnified pain.	Widespread stimulation produces a modest increase in pain.
Autonomic involvement	Autonomic features (e.g., nausea and sweating) frequently present.	Autonomic features less frequent.
Referred pain	Pain perceived at a site distant to the cause of the pain is common.	Pain is relatively well localised and 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 Aδ 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, viscero-muscular and musculo-visceral 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 chronic pelvic pain, ongoing tissue trauma, inflammation or infection is absent [60, 61]. However, conditions that produce recurrent trauma, infection or ongoing inflammation may result in chronic pelvic pain in a small proportion of cases. For example, out of a large cohort with acute bacterial prostatitis, 10.5% ended up with a state of CPPPS [62]. It is for this reason that the early stages of assessment include looking for these pathologies. Once excluded, ongoing investigations for these causes are rarely helpful and indeed may be detrimental.

When acute pain mechanisms are activated by a nociceptive event, as well as direct activation of the peripheral nociceptor transducers, sensitisation of those transducers may also occur; therefore, magnifying the afferent 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) [63].

There are a number of mechanisms by which the peripheral transducers may exhibit an increase in sensibility:

1. Modification of the peripheral tissue, which may result in the transducers being more exposed to peripheral stimulation.
2. There may be an increase in the chemicals that stimulate the receptors of the transducers [64].
3. There are many modifications in the receptors that result in them being more sensitive.

In general, the effect of 1 and 2 above is to lower the threshold and the effect of 3 above 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 [65, 66].

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.

Neuronal sensitisation 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. For example, for cutaneous stimuli, light touch would not normally produce pain, however, when central sensitisation is present, light touch may be perceived as painful (allodynia). In visceral hyperalgesia (so called because the afferents are primarily small fibres), visceral stimuli that are normally sub-threshold and not usually perceived, may be perceived and result in a sensation of fullness and a need to void or to defecate. Non-noxious stimuli may be interpreted as pain and stimuli that are normally noxious may be magnified (true hyperalgesia) with an increased perception of pain. As a consequence, one can see that many of the symptoms of PBPS and IBS may be explained by central sensitisation. A similar explanation exists for the muscle pain in FM.

It is now well accepted that there are both descending pain-inhibitory and descending pain-facilitatory pathways that originate from the brain [67]. Several neurotransmitters and neuromodulators are involved in descending pain-inhibitory pathways. The main ones 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 strength of 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.

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 [68]. 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 [69] 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 feeling pain from sensations that would not normally be experienced as painful.

An important review [31] of chronic pelvic pain in women dismantled the notion that women without relevant physical findings differ in psychological characteristics from women with relevant physical findings. Women with pelvic pain often have other non-pain somatic symptoms and current or lifetime anxiety and depression disorder [22]; they may have a history of physical or sexual abuse in childhood; but this is of unclear significance. Studies should avoid interpreting the absence of physical findings as evidence for psychological origins of the complaint ('psychosomatic' or 'somatoform' disorders). Pain studies describe multiple processes by which pain may spread across sites, or in time, including central sensitisation (see previous section), viscero-visceral cross sensitisation in relation to multiple pain sites [70], activation of the hypothalamic-pituitary axis and dysregulation of serotonergic pathways [71] that can render pain levels responsive to stress. Some pain problems which affect sexual activity are diagnosed as sexual problems (e.g., 'dyspareunia') when pain is the central problem and is not contingent on sexual activity alone [72]. Better integration of sexology and mainstream psychology for pelvic pain in both men and women is needed, building on a biopsychosocial formulation [73, 74].

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 [75].

Understanding the psychological components of pain

Psychological processes of emotions, thought and behaviour involve distributed networks, whose interactions with pain processing are complex, producing inhibition and facilitation of signal processing, appraisal, and response. Models that integrate psychological factors involved in maintaining persistent pelvic and urogenital pain with current neurobiological understanding of pain are few, but the quality is high (see Section 3.1.5.1).

There is no evidence that women with CPPPS without physical findings are primarily presenting a psychological problem [31]. Anxiety and post-traumatic stress symptoms are common in some women with CPPPS [23, 76] and with vulvar pain [77], and may account for substantial variance in health status, treatment use and treatment outcome; for instance, women's expectations about vulvar pain on penetration predicted pain, sexual function and sexual satisfaction [78]. Negative investigative findings do not necessarily resolve women's anxieties about the cause of pain [79, 80] and anxiety often focuses on what might be 'wrong'. Depression may be related to pain in various ways, as described above. Until measures are available that are adequately standardised in patients with pain, assessment of anxiety and distress requires questions about the patient's beliefs about the cause of pain, the hope that diagnosis will validate pain, the struggle with unpredictability, and the implications of pain for everyday life [81, 82]. Reference to the studies of the IMMPACT group [83] 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 later with chronic pain syndromes [33]. The patient should be asked about adverse life events that may produce these biological responses and affect general psychological well-being [33, 84].

3.1.5.3 Clinical paradigms in visceral pain

Referred pain

Referred pain is frequently observed and its identification is important for diagnosis and treatment. Referral is usually somatic to somatic, or visceral to somatic. However, there is no reason why pain cannot also be perceived within the area of an organ with the nociceptive signal having arisen from a somatic area. Referred pain may occur as a result of several mechanisms but the main theory is one of convergence-projection. In the convergence-projection theory, 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 [63].

Hyperalgesia refers to an increased sensitivity to normally painful stimuli. In patients that have passed a renal stone, somatic muscle hyperalgesia is frequently present, even a year after expulsion of the stone. Pain to non-painful stimuli (allodynia) may also be present in certain individuals. Somatic tissue hyperaesthesia is associated with urinary and biliary colic, IBS, endometriosis, dysmenorrhoea, and recurrent bladder infections. Primary 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 neurons. Central sensitisation also stimulates efferent activity that could explain the trophic changes that are often found in the somatic tissues.

Musculo-skeletal system 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 ligaments and tendons to the bones (enthesitis) and of the bursa (bursitis) may be found [85]. Certain postures affect the different muscles in different ways, and as a consequence, may exacerbate or reduce the pain. Stress, like negative sexual encounters, has been implicated as both an initiator of pelvic myalgia and as a maintenance factor.

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, PBPS 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 Primary prostate pain syndrome

There is only limited information on the true prevalence of PPPS in the population. As a result of significant overlap of symptoms with other conditions (e.g., benign prostatic enlargement and PBPS), purely symptom based case definitions may not reflect the true prevalence of PPPS [86, 87]. In the literature, population-based prevalence of prostatitis symptoms ranges from 2.2-14.2% [88, 89]. 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 Primary bladder pain syndrome

Reports of PBPS prevalence have varied greatly, along with the diagnostic criteria and populations studied. Recent reports range from 0.06-20% [90-96]. There is a female predominance of about 10:1 [94] but possibly no difference in race or ethnicity [86, 97, 98]. The relative proportions of Hunner's lesion and non-lesion disease are unclear. Incidence in studies has ranged from 5-50% [99-102]. There is increasing evidence that children under eighteen may also be affected, although prevalence figures are low; therefore, PBPS cannot be excluded on the basis of age [103].

3.2.2.3 Sexual pain syndrome

In the 1980s, an association between chronic pelvic pain and sexual dysfunction was postulated. In a review the relationship between Primary Prostate Pain Syndrome and health status, with influence on sexual activity, was addressed [104]. In a Chinese study of men with chronic pelvic pain, 1,768 males completed the questionnaires. The overall prevalence of sexual dysfunction was 49%. Erectile dysfunction (ED) is the most investigated sexual dysfunction in PPPS patients. The reported prevalence of ED ranges from 15.1-48%, varying with evaluation tools and populations [105, 106]. Erectile dysfunction was prevalent in 27.4% of Italian men aged 25-50 [107], 15.2% among Turkish men (significantly higher than in the control group) [108] and 43% among Finnish men with PPPS [109]. The prevalence of ED was found to be higher in young men with PPPS than in the general population. A significant correlation between "chronic prostatitis", chronic pelvic pain symptoms (measured by NIH-CPSI) and ED (measured by International Index of Erectile Function [IIEF]) was confirmed while other studies using the same questionnaires were not able to confirm such a correlation [74, 110]. Some studies also report ejaculatory dysfunction, mainly premature ejaculation [105, 106, 111, 112].

In community-based studies in the UK [113], New Zealand [114] and Australia [115], a substantially larger proportion of the women with chronic pelvic pain reported dyspareunia (varying between 29-42%) than women without chronic pelvic pain (varying between 11-14%). Only a few studies have investigated sexual problems within clinical populations [116]. Another study showed that all of the sexual function domains (desire, arousal, lubrication, orgasm, satisfaction, and pain) were significantly lower in women with chronic pelvic pain than in women without chronic pelvic pain [116]. One study of patients enrolled in chronic pain treatment programs in England has reported that 73% had pain-related sexual problems [117].

3.2.2.4 Myofascial pain syndromes

The relationship between muscular dysfunction (especially over-activity) and pelvic pain has been found in several studies [118]. Rectal pain treated with pelvic floor muscle therapy is only relieved when patients learn to relax their pelvic floor muscles [119, 120]. 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) [121]. This relationship has been found in chronic prostatitis [122], PBPS [123] and vulvar pain [124]. 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 shortened, leading to restrictions even in a relaxed state.

*3.2.3 **Influence on Quality of Life***

Data on the influence on QoL will be included in a future 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 Section 3.1.5.1. The underlying causes, including the mechanisms for the different clinical pain syndromes are described here.

3.2.5.1 Primary prostate pain syndrome

Pain is the main symptom in PPPS. As a common feature of primary chronic pain syndromes, no single aetiological explanation has been found. One explanation is that the condition probably occurs in susceptible men exposed to one or more initiating factors, which may be single, repetitive or continuous. Several of these potential initiating factors have been proposed, including infectious, genetic, anatomical, neuromuscular, endocrine, immune (including autoimmune), or psychological mechanisms. These factors may then lead to a peripheral self-perpetuating immunological, inflammatory state and/or neurogenic injury, creating acute and then chronic pain. A study showed that chronic but not acute histological inflammation of the prostate was significantly associated with symptomatic progression [125]. Based on the peripheral and the CNS, sensitisation involving neuroplasticity may lead to a centralised neuropathic pain state. This could also explain why tissue damage is not usually found in PPPS. There is growing evidence for a neuropathic origin and association with CNS changes of pain in PPPS, and anxiety appears to be a risk factor for its development [45].

3.2.5.2 Primary bladder pain syndrome

An initial unidentified insult to the bladder, leading to urothelial damage, neurogenic inflammation and pain is thought to be a trigger of PBPS. However, PBPS might be a local manifestation of a systemic disorder. No infection has as yet been implicated. Nevertheless, urinary infections are significantly more frequent during childhood and adolescence, in patients with PBPS in adulthood [126]. Experimental induction of chronic pelvic pain by O-antigen deficient bacterial strains supports the bacterial hypothesis [127]. Pancystitis, with associated perineural inflammatory infiltrates, and mast cell count increase is an essential part of PBPS type 3 C [128], but is rare in non-lesion PBPS [33, 68, 129, 130]. Cystoscopic and biopsy findings in both lesion and non-lesion PBPS are consistent with defects in the urothelial glycosaminoglycan (GAG) layer, which might expose submucosal structures to noxious urine components [131-135] and a consequent cytotoxic effect [136, 137]. Basic and clinical studies indicate that autonomic dysfunction with sympathetic predominance may be implicated in PBPS [138, 139].

An association has been reported between PBPS and non-bladder syndromes such as FM, CFS, IBS, vulvodynia, depression, panic disorders, migraine, sicca syndrome, temporomandibular joint disorder, allergy, asthma and systemic lupus erythematosus [140-145]. Psychological comorbidities, especially depression, has been found to be related to symptom severity [140]. Risk of PBPS correlates with a number of non-bladder syndromes in each patient [146]. Recent work showing non-lesion PBPS to have significantly more FM, migraine, temporomandibular joint disorder and depression than PBPS type 3 C patients, which emphasises, the need for subtyping [147].

3.2.5.3 Primary scrotal pain syndrome

Often scrotal pain is not associated with any specific pathology. Pain is perceived in the testes, epididymis, or the vas deferens. As the ilioinguinal, genitofemoral and the pudendal nerves intervate the scrotum [148], any pathology or intervention at the origin or along the course of these nerves may result in pain perceived in the scrotum [149].

Two special forms of scrotal pain syndrome can be described. The first is post-vasectomy scrotal pain syndrome which occurs following vasectomy. The mechanisms are poorly understood, and for that reason it is considered by some a special form of primary scrotal pain syndrome. Incidence of post-vasectomy pain is 2-20% among all men who have undergone a vasectomy. In men with post-vasectomy pain, 2-6% have a Visual Analogue Scale (VAS) score > 5 [150]. In a large cohort study of 625 men, the likelihood of scrotal pain after six months was 14.7%. The mean pain severity on a VAS score was 3.4/10. In the pain group, 0.9% had quite severe pain, noticeably affecting their daily life. In this cohort, different techniques were used to perform the vasectomy. The risk of post-vasectomy pain was significantly lower in the no-scalpel vasectomy group (11.7% vs. the scalpel group 18.8%) [151].

The second special form of scrotal pain is post-inguinal hernia repair pain. It is seen as a complication of hernia repair, but in trials it is seldom reported, or it is put under the term chronic pain (not specified). In studies that have explicitly mentioned scrotal pain, there was a difference in incidence between laparoscopic and open hernia repair. In almost all studies, the frequency of scrotal pain was significantly higher in the laparoscopic than in the open group [149, 152]. In one particular study, there was no difference at one year but after five years, the open group had far fewer patients with scrotal pain [153]. Inguinal hernia repair can lead to chronic post-surgical pain (CPSP) in up to 10% of patients at six months [154] and may present with groin and/ or scrotal pain. Testicular injury is uncommon (< 1%) but if associated with pain, orchidectomy can lead to symptomatic relief in 2/3 of patients [155]. Careful identification and preservation of nerves has been found to be associated with a reduced risk of chronic pain.

3.2.5.4 Primary urethral pain syndrome

Several mechanisms for the development of primary urethral pain syndrome have been proposed. The intimate relationship of the urethra with the bladder (both covered with urothelium) suggests that primary urethral pain syndrome may be a form of PBPS. Mechanisms thought to be basic for PBPS may also apply to the urethra. This means that the specific testing with potassium has been used to support the theory of epithelial leakage [156, 157]. Another possible mechanism is neuropathic hypersensitivity following urinary tract infection. The relationship with gynaecological and obstetric aspects is unclear. In a small group of patients with urethral pain, it has been found that grand multi-parity and delivery without episiotomy were more often seen in patients with urethral syndrome, using univariate analysis [158].

3.2.5.5 Primary vaginal and vulvar pain syndromes

Pain in the vagina or the female external genital organs is often due to infection or trauma, as a consequence of childbirth or surgery. Pain is usually a precedent to dyspareunia. When the pain persists for more than three months, it can be diagnosed as primary vulvar pain syndrome previously known as “vulvodynia” or “chronic vaginal pain” with no known cause. It is still a poorly understood condition, and therefore difficult to treat.

There are two main sub-types of primary 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 primary 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 primary 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 primary vulvar pain syndrome involve a complex interplay between affective, behavioural and interpersonal factors such as:
psychological factors, i.e. depressive symptoms, anxiety, pain-related fear and catastrophising [159, 160]

- history of physical or 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 Chronic pelvic pain and prolapse/Incontinence mesh

Continence and prolapse mesh implants were developed as simple flexible polypropylene plastic acting as a scaffold to treat stress urinary incontinence (SUI) and uterovaginal prolapse, respectively. They were deemed easy to insert, but no credence was given as to how safe they were, whether they could be removed should they cause complications, or what to do should they not be effective [161, 162]. Most meshes took less than an hour to implant surgically and most patients were treated as day cases, allowing women to leave hospital quickly and get on with their lives. Therefore, rather than undergo complex traditional surgery, women were

offered permanent mesh implants, particularly in the treatment of SUI where they were considered to be the gold standard [163, 164]. However, over the last few years the insertion of mesh has come with significant 'health and safety warnings' [165, 166].

For many, mesh was initially seen not just as an effective treatment but as a permanent one. Complications were not thought to be a significant issue and the figure of 1-3% was often quoted. However, we now know the complication rate was closer to 10% [167]. They included chronic pain [168, 169], as well as chronic infections [170], erosion into the surrounding organs including the vagina, urethra and bladder, as well as nerve and musculoskeletal damage affecting mobility [168, 169, 171, 172]. All had a significant impact on the patients' QoL.

It is as a result of severely debilitating complications following mesh implantation [168], that the field of mesh removal medicine and surgery emerged [173].

Early recognition of possible mesh complications is very important. It is normal to wake up in some degree of discomfort after any surgery. However, if the pain after the operation is very severe and much more than expected after this type of surgery, it can be a sign that there was added trauma to the surrounding organs during the procedure. Most pain is often managed with analgesia, but some women might not fully respond to therapy. If the pain is difficult to treat and does not improve over time, it may become necessary to remove the mesh. Leaving a painful mesh in the pelvis, can lead to chronic pelvic pain. The precise mechanism is unknown but it is thought to be a 'neuro-inflammatory' process [174], as has been proposed in hernia mesh neuralgia. The impact of the mesh, regardless of site, appears to be similar.

3.2.5.7 Chronic post-surgical pain

Chronic post-surgical pain

Chronic pain may develop following surgical procedures and has a significant impact on the individual. The ICD-11 has recently classified chronic post-surgical pain (CPSP) as a chronic pain condition. The definition of CPSP is chronic pain that develops or increases in intensity after a surgical procedure and persists beyond the healing process, i.e., at least three months after the surgery [175].

Chronic post-surgical pain may occur in a significant number of patients, and is more prevalent following some operations rather than others. Procedures with a higher risk of CPSP include limb amputation (30-85%), thoracotomy (5-65%) and mastectomy (11-57%) [176].

Risk factors for CPSP include a number of pre-, peri- and post-operative factors. Younger age, female gender, chronic pain pre-operatively elsewhere, higher number of previous operations, use of opioids and a higher post-operative pain score have been found to be associated with a higher risk of CPSP in a prospective cohort of patients undergoing laparoscopy and laparotomies. Older age, malignant indication for surgery, a higher pre-operative mental health score and the use of epidural analgesia in addition to general anaesthesia were protective [177, 178].

There are a number of procedures specific to the abdomen and pelvis that are associated with an increased risk of chronic pain post-surgery, including bariatric procedures, inguinal hernia repair, vasectomy, hysterectomy and caesarean section. Adhesions are a common cause of chronic abdominal pain but despite this, a SR identified only low level evidence to help guide management of affected individuals [179].

The estimated prevalence of CPSP following bariatric surgery is 30% [180]. In affected individuals careful assessment that may include laparoscopy could identify a treatable cause (such as adhesions, mesenteric defect or cholecystitis) and lead to a significant reduction in post-operative pain [181].

Inguinal hernia repair can lead to CPSP in up to 10% of patients at six months [154] and may present with groin and/or scrotal pain. The incidence of post-vasectomy pain ranges from 2-20% [150, 182]. The risk is significantly lower following the no scalpel technique [151].

The incidence of post-surgical pain following hysterectomy is difficult to determine as pain is a common indication for the operation. When defined as CPSP, rates are estimated at 28-30% [183, 184]. Careful case selection and management of patient expectation is therefore important.

The frequency of caesarean section has increased over time. A meta-analysis has shown a significant incidence of CPSP both at three months and at more than twelve months (15% and 11% respectively) [185], therefore careful counselling is needed in non-emergency cases.

3.2.5.8 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, trauma, surgical incisions and post-operative scarring may result in nerve injury [186].

Pudendal neuralgia is the most often mentioned form of nerve damage in the literature. Anatomical variations may pre-dispose the patient to developing pudendal neuralgia over time or with repeated low-grade trauma (such as sitting for prolonged periods of time or cycling) [187, 188].

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.
5. The site of injury determines the location 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. It is suggested 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 [189]. 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 [190, 191]. The surgery itself may also directly damage the nerve. Pelvic surgery such as sacrospinous fixation is clearly associated with pudendal nerve damage in some cases [192, 193]. In many types of surgery, including colorectal, urological and gynaecological, pudendal nerve injury may be implicated.
- Fractures of the sacrum or pelvis may result in pudendal nerve/root damage and pain. Falls and trauma to the gluteal region may also produce pudendal nerve damage if associated with significant tissue injury or prolonged pressure.
- Tumours in the pre-sacral space must be considered. Tumours invading the pudendal nerve may occur and there may also be damage from surgery for pelvic cancer [194].
- 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 [195].
- Child birth and repeated abdominal straining associated with chronic constipation [196] are thought to pre-dispose elderly women to post-menopausal pelvic floor descent and stretching of the pudendal nerve with associated pain. Changes in the hormone status may also be a factor. In Urogenital Pain Management Centres, the commonest associations with pudendal neuralgia appear to be: history of pelvic surgery; prolonged sitting; and post-menopausal older women.

Sexual dysfunction

Chronic pelvic pain is a clinical condition that results from complex interactions of physiological and psychological factors and has a direct impact on the social, personal and professional lives of men and women.

Men

Men

Chronic pain as well as its treatment can impair our ability to express sexuality. In an England study, 73% of patients with any chronic pain had some degree of sexual problems as a result of the pain [117]. These problems can occur because of several factors. Psychological factors like pain catastrophising, a decrease in self-esteem, depression and anxiety can contribute to the problem severity [197]. Physiological factors like fatigue, nausea and pain itself can cause sexual dysfunction. Pain medications (opioids, and the selective serotonin re-uptake inhibitors [SSRIs]) can also decrease libido [198] and delay ejaculation. The number of

studies on the effects of CPPPS on sexual function is limited. Sexual dysfunction is often ignored because of a lack of standardised measurements. At present, the most commonly used tool is the IIEF questionnaire [110].

The presence of pelvic pain may increase the risk for ED independent of age [199]. On the other hand, cross-sectional data suggest no improvement of lower urinary tract symptoms (LUTS) by an increased frequency of ejaculation [200]. Although mental distress and impaired QoL related to illness could contribute to sexual dysfunction observed in patients with PPPS, the presence of erectile and ejaculatory disorders is more frequently related to symptoms suggestive of a more severe inflammatory condition [112]. These arguments are important for the understanding of the close relationship between CPPPS symptoms, disturbed sexuality, impact on QoL, and psychological implications including depression and more failure anticipation thoughts [104-106, 200-202]. 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 CPPPS have reported a high frequency of sexual relationship dissolution and psychological symptoms, such as depression and suicidal thinking [104, 203]. On the other hand, it was found that men with PPPS did not report significantly decreased sexual satisfaction compared to controls [204]. There is consensus that therapeutic strategies reducing symptoms of pelvic pain are of relevance in relation to changes in sexual function. Also intimacy and having sex can yield positive experiences that will reduce the pain. The CNS plays an important role in this mechanism.

Women

Chronic pelvic pain leads to substantial impairment in QoL and several sexual dysfunctions [205]. It seems reasonable to expect that pain, extreme fatigue, depressive mood and pain drugs will affect women's sexuality. Women with CPPPS 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 CPPPS reported significantly more sexual avoidance behaviour, non-sensuality, and complaints of "vaginismus" [206]. Patients with CPPPS reported more sexual problems than women with any other type of chronic pain problem [207]. The quality of intimate relationships is closely connected with sexual function [208]. Satisfaction with sexual relationships appears to be associated with higher marital functioning [209]. In addition sexual dissatisfaction is related to sexual dysfunction. When one partner suffers from chronic pain, the ability of both partners to cope with the pain and the extent to which partners are supportive of the chronic pain sufferer have been found to be a predictor of sexual functioning [209].

Approximately two-thirds of patients in another study reported reduced frequency in their sexual relations as a result of CPPPS [210]. One study demonstrated that CPPPS 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 CPPPS [211]. In an interview with 50 chronic pain sufferers and their spouses, 78% of the pain sufferers and 84% of partners described deterioration, including cessation of their sex life [212]. In a study in patients with back pain, half reported decreased frequency of sex since the onset of chronic pain [117]. The Female Sexual Function Index (FSFI) has been developed as a brief, multi-dimensional self-report instrument for assessing the key dimensions of sexual function in women, which includes desire, subjective arousal, lubrication, orgasm, satisfaction, and pain. Using the FSFI, women with CPPPS reported worse sexual function in all subscales and total score than women without CPPPS. The largest differences between women with CPPPS and without CPPPS, 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 CPPPS. The FSFI also showed good ability to discriminate between women with and without CPPPS [211].

Myofascial pain

Myalgia is too often overlooked as a form of chronic pelvic pain. The pelvic floor and adjacent muscles are used in an abnormal way. Studies in the field of chronic prostatitis support the idea that patients with CPPPS have more muscle spasm and increased muscle tone and report pain when the pelvic floor muscles are palpated [213]. Learning pelvic floor muscle relaxation can diminish spasm and pain [214]. Repeated or chronic muscular overload can activate trigger points in the pelvic floor muscles. 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 CPPPS group [122].

The first ideas about the neurological aspects of the pelvic floor muscles in relation to chronic pelvic pain were published in 1999. The possibility of CNS changes in the regulation of pelvic floor function was suggested as a mechanism for development of CPPPS. Of the patients presenting with pelvic pain, 88% had poor to absent pelvic floor muscle function [121]. Animal 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 [215].

Repeated or chronic muscular overload can activate trigger points in the muscle. Trigger points are defined as hyper-irritable spots within a taut band. Other criteria for trigger points are recognition of the pain as 'familiar', and pain on stretching the muscle. Apart from pain, trigger points prevent full lengthening of the muscle, thereby restricting the range of movement. Pain as a result of these trigger points is aggravated by specific movements and alleviated by certain positions. Positions and movements in which the shortened muscle is stretched are painful. Patients know which activities and postures influence pain. Trigger points can be located within the pelvic floor muscles and in adjacent muscles such as the abdominal, gluteal and iliopsoas muscles. Pain is aggravated by pressure on the trigger point (e.g., pain related to sexual intercourse). Pain also worsens after sustained or repeated contractions of pelvic floor muscles (e.g., pain related to voiding or defecation).

3.3 Abdominal aspects of pelvic pain

3.3.1 ***Incidence***

Epidemiological data on IBS and CPPPS are scarce [216]. Chronic Pelvic Pain has been shown to be one of the most common functional disorders in women of reproductive age. The monthly incidence rate of CPPPS published by Zondervan *et al.* was 1.58/1000 [217].

3.3.2 ***Prevalence***

Using a vague definition of continuous or episodic pa*in situ*ated below the umbilicus over six months, one study reported that CPPPS was one of the most common diagnoses in primary care units in Great Britain [217]. The monthly prevalence rate of CPPPS in this study was 21.5/1,000, with an annual prevalence of 38.3/1,000. The prevalence rates increase significantly with older age and vary significantly between regions in the UK. The overall prevalence of anorectal pain in a sample of USA householders was 11.6% for functional anorectal pain and 6.6% for Levator Ani Syndrome. The difference between male and female was small (11.1 vs 12.1%) [218]. Irritable bowel syndrome is associated with common gynaecologic problems (endometriosis, dyspareunia, and dysmenorrhoea) [219]. Fifty per cent of women who presented with abdominal pain to the gynaecologic clinic or were scheduled for laparoscopy due to CPPPS had symptoms of IBS [220]. In a survey from Olmsted county, 20% of women reported CPPPS and 40% of those met the criteria for IBS [221]. This overlap of CPPPS 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 [222]. Clinical features of pelvic floor dysfunction, gynaecological and psychological features, are related to disordered anorectal function in IBS patients, but do not predict physiological anorectal testing.

3.3.3 ***Influence on Quality of Life***

There is little known on health related quality of life (HRQoL) in patients with CPPPS. There is a need to develop validated disease specific HRQoL instruments for CPPPS in addition to sound measurement properties. More data are available in patients with IBS treated at referral centres who have comparable HRQoL scores as patients with other common disorders such as diabetes, end-stage renal disease, and inflammatory bowel disease [223]. Sub-groups of IBS with predominance of diarrhoea or constipation show no difference in HRQoL. Multi-variate analysis shows that HRQoL in patients with IBS is affected by sex and psychological conditions.

3.3.4 ***Costs***

Costs combine direct health-care costs and societal costs (productivity loss) such as under-performance and absenteeism from work. The annual costs to society can be calculated by using the average population earnings. In Germany direct care costs are estimated at €791 and societal costs €995 per patient with IBS per year which may be comparable to patients with CPPPS [224].

3.3.5 ***Risk factors & underlying causes***

Risk factors are covered in Section 3.1.5.

3.4 Summary of evidence and recommendations: CPPPS and mechanisms

Summary of evidence	LE
CPPPS 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 CPPPS as a pain syndrome is essential as it encourages a holistic approach to management with multi-specialty and multi-disciplinary care.	2

Recommendations	Strength rating
All of those involved in the management of chronic pelvic pain should have knowledge of peripheral and central pain mechanisms.	Strong
The early assessment of patients with chronic pelvic pain should involve investigations aimed at excluding disease-associated pelvic pain.	Strong
Assess functional, emotional, behavioural, sexual and other quality of life issues, such as effect on work and socialisation, early in patients with chronic pelvic pain and address these issues as well as the pain.	Strong
Build up relations with colleagues so as to be able to manage CPPPS comprehensively in a multi-specialty and multi-disciplinary environment with consideration of all their symptoms.	Strong

4. DIAGNOSTIC EVALUATION

4.1 General evaluation

4.1.1 History

History is very important for the evaluation of patients with chronic pelvic pain. Pain syndromes are symptomatic diagnoses, which are derived from a history of pain perceived in the region of the pelvis, and absence of other pathology, for a minimum of three months. This implies that specific disease-associated pelvic pain caused by bacterial infection, cancer, drug-induced pathology (e.g., ketamine use) [225], 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 difficult to interpret in chronic pelvic pain [226].

Anxiety about pain often refers to fears of missed pathology (particularly cancer) as the cause of pain [37], or to uncertainties about treatment and prognosis. These can drive healthcare seeking behaviour. The question: "What do you believe or fear is the cause of your pain?" has been suggested [227]. Anxiety may also concern urinary urgency and frequency that are problematic in social settings.

Depression or depressed moods are common in chronic pain [228], often related to losses consequent to chronic pain (work, leisure activities, social relationships, etc.). Due to the lack of suitable assessment instruments, it is better to ask a simple question such as "How does the pain affect you emotionally?" If the answer gives cause for concern about the patient's emotional state, further assessment should be undertaken by an appropriately qualified colleague.

Most measures of restricted function are designed primarily for musculoskeletal pain and may emphasise mobility problems rather than the difficulties of the individual with pelvic or urogenital pain. A promising specific measure, UPOINT, was introduced and in a later version the sexological aspects were added [229]. However, it may underassess relevant psychological variables [44]. Generic QoL measures are helpful. If such an instrument

is not already used in the clinic, the Brief Pain Inventory [230] provides a broad and economical assessment of interference of pain with various aspects of life, and is available in multiple languages. (For further suggested instruments see [231]).

4.1.1.2 Urological aspects

Pain may be associated with urological symptoms. A detailed history of LUT functions should be taken. Dysfunctions of the LUT may exacerbate symptoms, as pain may interfere with the function of the LUT. Micturition in all its aspects should be addressed. Special attention should be paid to the influence of micturition on the experience of pain.

Primary prostate pain syndrome

Primary prostate pain syndrome is diagnosed from a history of pain perceived in the region of the prostate (convincingly reproduced by prostate palpation), and absence of other LUT pathology, for a minimum of three 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 PPPS. 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 [50]. In addition, associated LUT 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.

Primary bladder pain syndrome

Primary bladder pain syndrome should be diagnosed on the basis of pain, pressure or discomfort associated with the urinary bladder, accompanied by at least one other symptom, such as daytime and/or night-time increased urinary frequency, the exclusion of confusable diseases as the cause of symptoms, and if indicated, cystoscopy with hydrodistension and biopsy (Table 4) [16].

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 [232, 233];
4. aggravated by food or drink [233].

Primary bladder pain syndrome type 3 can lead to a small capacity fibrotic bladder with or without upper urinary tract outflow obstruction.

4.1.1.3 Gynaecological aspects

A detailed medical history outlining the nature, frequency and site of pain; its relationship to precipitating factors and the menstrual cycle, may help define the aetiology. A menstrual and sexual history, including a history of sexually transmitted diseases, vaginal discharge, as well as previous sexual trauma is mandatory as well as up to date cervical cancer screening. A history of obstetric and/or gynaecological surgery is also warranted, particularly if devices such as synthetic mesh were used.

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 IV 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 primary chronic anal pain syndrome (chronic proctalgia) according to the Rome IV criteria are as follows and must include all of the following: chronic or recurrent rectal pain or aching, episodes last at least thirty minutes and exclusion of other causes of rectal pain such as ischaemia, inflammatory bowel disease, cryptitis, intramuscular abscess and fissure, haemorrhoids, prostatitis, and Coccyx Pain Syndrome. These criteria should be fulfilled for the past three months with symptom onset at least six months before diagnosis [17, 234].

The primary 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 over-activity of the pelvic floor muscles and probably recto-anal incoordination.

Primary intermittent chronic anal pain syndrome (proctalgia fugax) consists of all the following diagnostic criteria, which should be fulfilled for three months: recurrent episodes of pain localised to the anus or lower rectum, episodes last from several seconds to minutes and there is no anorectal pain between episodes. Stressful life events or anxiety may precede the onset of the intermittent chronic anal pain syndrome. The attacks may last from a few seconds to as long as 30 minutes. 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 type of pressure being applied, either directly to the nerve or indirectly to other tissue, resulting in pudendal traction. Allodynia is pain on light touch due to involvement of the CNS, and may make sexual contact and the wearing of clothes difficult. These patients often remain standing, and as a consequence, develop a wide range of other aches and pains. Soft seats are often less well-tolerated, whereas sitting on a toilet seat is said to be much better tolerated. If unilateral, sitting on one buttock is common. The pain may be exacerbated by bowel or bladder evacuation.

Pudendal nerve damage may be associated with a range of sensory phenomena. In the distribution of the nerve itself, as well as unprovoked pain; the patient may have paraesthesia (pins and needles); dysaesthesia (unpleasant sensory perceptions usually but not necessarily secondary to provocation, such as the sensation of running cold water); allodynia (pain on light touch); or hyperalgesia (increased pain perception following a painful stimulus, including hot and cold stimuli). Similar sensory abnormalities may be found outside of the area innervated by the damaged nerve, particularly for visceral and striated muscle hyperalgesia.

The cutaneous sensory dysfunction may be associated with superficial dyspareunia, but also irritation and pain associated with clothes brushing the skin. There may also be a lack of sensation and pain may occur in the presence of numbness. Visceral hypersensitivity may result in an urge to defecate or urinate. This is usually associated with voiding frequency, with small amounts of urine being passed. Pain on visceral filling may occur. Anal pain and loss of motor control may result in poor bowel activity, with constipation and/or incontinence. Ejaculation and orgasm may also be painful or reduced.

Many of those suffering from pudendal neuralgia complain of fatigue and generalised muscle cramps, weakness and pain. Being unable to sit is a major disability, and over time, patients struggle to stand and they often become bedbound. The immobility produces generalised muscle wasting, and minimal activity hurts. As a consequence of the widespread pain and disability, patients often have emotional problems, and in particular, depression. Patients with chronic pelvic pain are also often anxious and have the tendency to catastrophise. Depression, catastrophising and disability are all poor prognostic markers. Cutaneous colour may change due to changes in innervation but also because of neurogenic oedema. The patient may describe the area as swollen due to this oedema, but also due to the lack of afferent perception.

4.1.1.6 Myofascial aspects

When taking a history from a patient with pelvic pain, it is important to address the function of all the organs in the pelvic area. The following items certainly should be addressed: lower urinary tract function, anorectal function, sexual function, gynaecological items, presence of pain and psychosocial 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. 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 CPPPS, 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. It is important to look for abnormalities in muscle function.

Examination of the external genitalia is a part of the evaluation. In patients with scrotal pain, gentle palpation of each component of the scrotum is performed to search for masses and painful spots. The penis and urethra may be palpated in a similar way. Many authors recommend that one should assess cutaneous allodynia along the dermatomes of the abdomen (T11-L1) and the perineum (S3), and the degree of tenderness should be recorded. The bulbocavernosus reflex in the male may also provide useful information concerning the intactness of the pudendal nerves. Clinical pelvic examination should be a single digit examination if possible. The usual bi-manual 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 as well as the ability to contract and relax these muscles.

At clinical examination, perianal dermatitis may be found as a sign of faecal incontinence or diarrhoea. Fissures may be easily overlooked and should be searched for thoroughly in patients with anal pain. A 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 musculo-skeletal, 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 ischial 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 abdominis or paraspinal muscles).

4.2 Supplemental evaluation

If history is suggestive of lower urinary tract, gynaecological, anorectal or other disease of known aetiology, diagnostic work-up should follow respective guidelines.

*4.2.1 **Assessing pelvic pain and related symptoms***

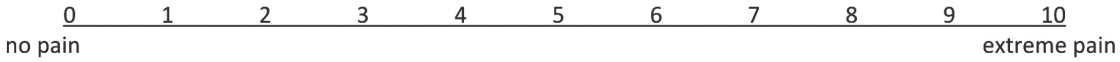
Determination of the severity of pain and associated symptoms, its progression and treatment response can be assessed only by means of a reliable and validated symptom-scoring instrument. These subjective outcome measures are recommended for the basic evaluation and therapeutic monitoring of patients. Pain should always be assessed at presentation and (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.

Quality of life should also be measured because it can be very poor compared to other chronic diseases [235, 236]. In a study 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) [57].

Where the primary outcome of treatment is pain relief, it is useful before starting treatment to agree a clinically useful level of relief [237]. The most reliable methods are:

- a five point verbal scale: none, mild, moderate, severe, very severe pain;
- a VAS score from one to ten;
- an eleven point numerical scale (as below).



Pain assessment ratings are not independent of cognitive and emotional variables [56]. 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 [237].

Primary prostate pain syndrome

Reliable, valid indices of symptoms and QoL are the NIH-CPSI [238] and the International Prostate Symptom Score (I-PSS) [239].

Primary 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 [240].

Gastrointestinal questionnaire

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 [241, 242]. 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 the most frequent effects on sexual function are ED and premature ejaculation. These can be evaluated by proper questionnaires namely IIEF and PEDT (Premature Ejaculation Diagnostic Tool). In comparison with controls, women with chronic pelvic pain reported significantly more sexual avoidance behaviour, non-sensuality, and complaints of "vaginismus" [196]. The Female Sexual Function Index (FSFI) has been developed as a brief, multi-dimensional self-report instrument for assessing the key dimensions of sexual function in women, which includes desire, subjective arousal, lubrication, orgasm, satisfaction, and pain. The corresponding evidence in men is lacking.

*4.2.2 **Focused myofascial evaluation***

Pelvic floor muscle testing can be done by the medical doctor but a consultation of the pelvic floor by a physiotherapist is a good alternative, but either should have had appropriate training in pelvic assessment. 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 validity and intra-observer reliability. It can therefore be considered suitable for use in clinical practice [243]. Rectal examination is a good way to test the pelvic floor function in men [244]. There is a growing number of reports on the use of ultrasound (US) in establishing the function of the pelvic floor muscles. The exact place in the diagnostic setting needs to be addressed in the future [245]. In a cohort study of 72 men with chronic pelvic pain, 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%) [246]. In addition, a broad musculoskeletal (tender point) evaluation, including muscles outside the pelvis, helps to diagnose the myofascial pain aspects of the pelvic pain in phenotyping pelvic pain patients [247, 248].

*4.2.3 **Neurological***

Injections

An injection of local anaesthetic and steroid at the site of nerve injury may be diagnostic. Differential block of the pudendal nerve helps to provide information in relation to the site where the nerve may be trapped [249, 250]. Infiltration at the ischial spine requires the use of a nerve stimulator/locator. Both motor (anal contraction) and sensory endpoints may be noted. The anatomical target may be localised by fluoroscopy, computed tomography (CT) guidance, or the use of US. Ultrasound avoids any form of radiation, whereas CT guidance involves a significant amount of radiation. As well as injecting around the pudendal nerve, specific blocks of other nerves arising from the pelvis may be performed.

Electrophysiological studies

These may reveal signs of perineal denervation, increased pudendal nerve latency, or impaired bulbocavernosus reflex [251, 252]. 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 CPPS. Once the latter diagnosis is established, studies can be useful to assess functional abnormalities and phenotype conditions such as PBPS, and primary chronic anal pain syndrome.

Ultrasound

Ultrasound has limited value but may reassure patients. However, over-investigating may be detrimental.

MRI

Magnetic resonance neurography has been increasingly used in specialised centres for the diagnosis of the location (proximal vs. peripheral) and degree (total vs. partial) of nerve injury in the peripheral nervous system, earlier and with higher specificity than conduction studies. This may show benefits for CPPPS in the coming years.

MR defecating proctogram

Magnetic resonance imaging in conjunction with MR defecography has become the most valuable imaging technique to assess anorectal function dynamically. Magnetic resonance imaging studies simultaneously outline 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 or supine position and the limited space for the patient, which may reduce the ability to strain and thereby reduce the sensitivity of the method, underestimating the size of entero- and rectoceles as well as the amount of intussusception.

Functional neuroimaging

Functional neuroimaging, functional magnetic resonance imaging (fMRI) is currently being re-evaluated as a research tool and some groups have raised issues around over interpretation [253]. With regards to pain, fMRI findings may represent a pain matrix or may represent non-specific threat processing [254]. Currently this panel cannot recommend fMRI as a clinical tool [255].

*4.2.5 **Laboratory Tests***

Microbiology tests

Primary prostate pain syndrome

Laboratory diagnosis of prostatitis has been classically based on the four-glass test for bacterial localisation [256]. Besides sterile pre-massage urine (voided bladder urine-2), PPPS shows < 103 cfu/mL of uropathogenic bacteria in expressed prostatic secretions and insignificant numbers of leukocytes or bacterial growth in ejaculates. However, this test is too complex for use by practising urologists. Diagnostic efficiency may be enhanced cost-effectively by a simple screening procedure, that is, the two-glass test or pre-post-massage test (PPMT) [257, 258]. Overall, these tests help only a little in the diagnosis of PPPS, because 8% of patients with suggested PPPS have been found to have positive prostatic localisation cultures, similar to the percentage of asymptomatic men [259].

Primary bladder pain syndrome

Urine dipstick and urine culture (including culture for Tuberculosis if sterile pyuria) are recommended in all patients suspected of having PBPS. Urine cytology is also recommended in risk groups.

Gynaecological aspects of chronic pelvic pain

Vaginal and endocervical swabs to exclude infection are recommended. In specific cases, imaging may be required to help rule out a defined pathology such as sacral neuropathy in endometriosis [260]

*4.2.6 **Invasive tests***

Anorectal pain

Anorectal manometry with sensory testing (pressure volume measurement: barostat) may be useful to diagnose dyssynergic defecation and hypersensitivity of the rectum which are typical for patients with CPPPS and IBS. Anorectal manometry and the ballon expulsion test (BET) may also help to predict the response to biofeefback therapy in Levator Ani Syndrome [119]. Flexible rectosigmoidoscopy or colonoscopy should be considered in patients with anorectal pain to rule out coincidental colorectal pathology.

Laparoscopy for females

Laparoscopy is perhaps the most useful invasive investigation to exclude gynaecological pathology [261, 262] and to assist in the differential diagnosis of CPPPS in women [263, 264]. Often, it is combined with cystoscopy [265, 266] 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 [267]. Integrating somatic and psychological assessment from the start rather than dealing with psychological concerns only after excluding organic causes of pelvic pain is helpful [268].

Cystoscopy and bladder biopsy

Despite controversy on the diagnostic and follow-up value of cystoscopy in PBPS [269-273] the 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) [274]. Endoscopically, PBPS 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's lesion [232]. The scar ruptures with increasing bladder distension, producing a characteristic waterfall type of bleeding. There is a strong association between PBPS type 3 and reduced bladder capacity under anaesthesia [275]. 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 PBPS [276]. Biopsies are helpful in establishing or supporting the clinical diagnosis of both classic and non-lesion types of the disease [131, 156, 274, 277, 278]. Important differential diagnoses to exclude, by histological examination, are carcinoma *in situ* and tuberculous cystitis [279].

Table 4: ESSIC classification of PBPS types according to results of cystoscopy with hydrodistension and biopsies [16]

	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

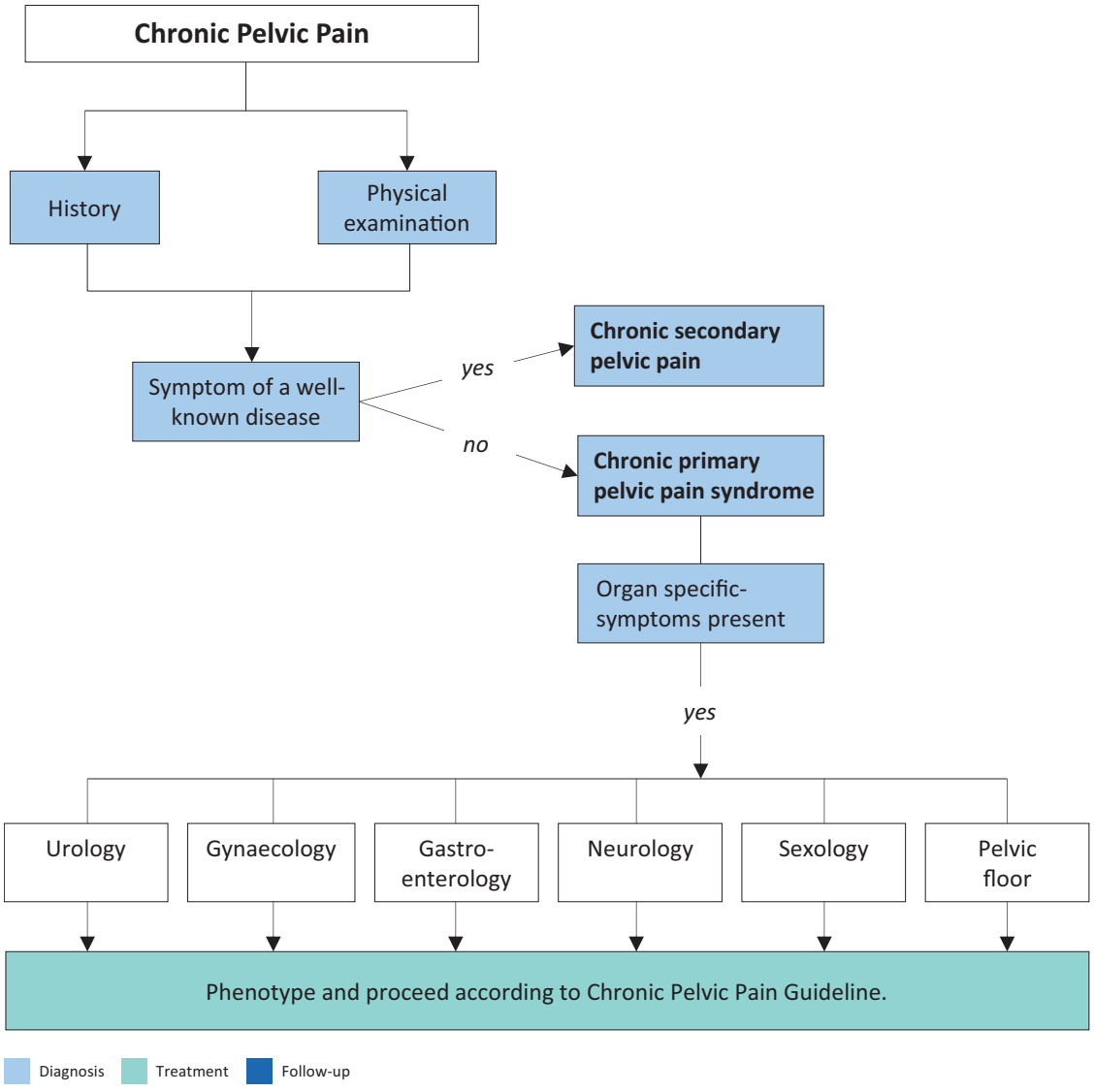


Figure 2: Phenotyping of pelvic pain - UPOINT classification

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.
Sexological	Erectile function, ejaculatory function, post-orgasmic pain.

4.4 Other painful conditions without a urological cause

Dysmenorrhoea

Menstrual pain or 'dysmenorrhoea' may be primary or secondary. Primary dysmenorrhoea classically begins at the onset of ovulatory menstrual cycles and tends to decrease following childbirth [263]. Secondary dysmenorrhoea suggests the development of a pathological process, such as endometriosis [262], adenomyosis or pelvic infection, which need to be excluded.

Infection

In pre-menopausal women, a history of Pelvic Inflammatory Disease (PID) must be excluded. A patient's sexual history should be taken along with swabs to exclude chlamydia and gonorrhoea infection. Bacterial and viral genital tract pathogens should also be excluded [280], as they can cause severe pelvic/vaginal/vulvar pain [281] and are associated with ulcerating lesions and inflammation, which may lead to urinary retention [282]. If there is any doubt about the diagnosis, laparoscopy may be helpful, as one of the differential diagnoses is endometriosis.

Endometriosis and adenomyosis

The incidence of endometriosis is rising in the developed world. It has widespread impact on women's lives [283], with pain more important than physical findings in determining QoL [284]. The precise aetiology is unknown, but an association with infertility is recognised [285]. A diagnosis is usually made when a history of secondary dysmenorrhoea and/or dyspareunia exists [286]. 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 [287]. Adenomyosis is associated with augmented pain during menses [288]. It is diagnosed by an US scan of the uterus, which often shows cystic dilatation of the myometrium [289].

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 chronic pelvic pain related to the site of injury [290]. Female sexual dysfunction is perhaps the commonest presenting problem [291], though increasingly women are reporting other symptoms such as pelvic girdle pain and other genito-pelvic pain of different aetiology [292]. There is often a transient problem with oestrogen deficiency in the post-partum period and during breastfeeding, which can compound this situation. Denervation of the pelvic floor can similarly compound the situation [293].

Pain associated with pelvic organ prolapse and prolapse surgery
Pelvic organ prolapse is often asymptomatic, unless it is so marked that it causes back pain, vaginal pain and skin excoriation [294]. 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 has entailed the use of non-absorbable mesh (usually in the form of "mesh kits"). Although they may have a role in supporting the vagina, they are also associated with several complications including bladder, bowel and vaginal trauma [295], chronic pain [296] and neuropathy [297]. Patients need to be fully evaluated and may need specialised imaging, using contrast mediums if necessary, to make a diagnosis of the possible cause of the pain [298-301].

Haemorrhoids
Chronic pelvic pain is rare in haemorrhoidal disease because endoscopic and surgical treatment is mostly effective in acute disease. The most frequent aetiology of pain without significant bleeding is thrombosed external haemorrhoids or an anal fissure. Haemorrhoidal pain on defecation associated with bleeding is usually due to prolapse or ulceration of internal haemorrhoids. Anaemia from haemorrhoidal bleeding is rare but may arise in patients on anti-coagulation therapy, or those with clotting disorders.

Anal fissure
Anal fissures are tears in the distal anal canal and induce pain during and after defecation. The pain can last for several minutes to hours. Persistence of symptoms beyond six weeks or visible transversal anal sphincter fibres define chronicity. Fissures located off the midline are often associated with specific diseases such as Crohn's disease or anal cancer. Internal anal sphincter spasms and ischaemia are associated with chronic fissures.

Proctitis
Abdominal and pelvic pain in patients with inflammatory bowel disease and proctitis are often difficult to interpret. Faecal calprotectin may help to differentiate between inflammation and functional pain, to spare steroids.

Irritable bowel syndrome
Although IBS can be associated with pelvic pain, the panel consider a full discussion of this topic beyond the scope of these guidelines. A number of high quality clinical guidelines address this topic [234, 302].

4.5 Summary of evidence and recommendations: diagnostic evaluation

4.5.1 Diagnostic evaluation - general

Summary of evidence	LE
Clinical history and examination are mandatory when making a diagnosis.	2a

Recommendation	Strength rating
Take a full history and evaluate to rule out a treatable cause in all patients with chronic pelvic pain.	Strong

4.5.2 Diagnostic evaluation of primary prostate pain syndrome

Summary of evidence	LE
Primary prostate pain syndrome is associated with negative cognitive, behavioural, sexual, or emotional consequences, as well as with symptoms suggestive of LUT and sexual dysfunction.	2b
Primary prostate pain syndrome has no known single aetiology.	3
Pain in PPPS involves mechanisms of neuroplasticity and neuropathic pain.	2a
Primary prostate pain syndrome has a high impact on QoL.	2b
Depression and catastrophic thinking are associated with more pain and poorer adjustment.	3
The prevalence of PPPS-like symptoms is high in population-based studies (> 2%).	2b
Reliable instruments assessing symptom severity as well as phenotypic differences exist.	2b

Recommendations	Strength rating
Adapt diagnostic procedures to the patient. Exclude specific diseases with similar symptoms.	Strong
Use a validated symptom and quality of life scoring instrument, such as the National Institutes of Health Chronic Prostatitis Symptom Index, for initial assessment and follow-up.	Strong
Assess primary prostate pain syndrome-associated negative cognitive, behavioural, sexual, or emotional consequences, as well as symptoms of lower urinary tract and sexual dysfunctions.	Strong

4.5.3 Diagnostic evaluation of primary bladder pain syndrome

Summary of evidence	LE
Primary bladder pain syndrome has no known single aetiology.	3
Pain in PBPS does not correlate with bladder cystoscopic or histologic findings.	2a
Primary bladder pain syndrome Type 3 C can only be confirmed by cystoscopy and histology.	2a
Lesion/non-lesion disease ratios of PBPS are highly variable between studies.	2a
The prevalence of PBPS-like symptoms is high in population-based studies.	2a
Primary bladder pain syndrome occurs at a level higher than chance with other pain syndromes.	2a
Primary bladder pain syndrome has an adverse impact on QoL.	2a
Reliable instruments assessing symptom severity as well as phenotypical differences exist.	2a

Recommendations	Strength rating
Perform general anaesthetic rigid cystoscopy in patients with bladder pain to subtype and rule out confusable disease.	Strong
Diagnose patients with symptoms according to the EAU definition, after primary exclusion of specific diseases, with primary bladder pain syndrome (PBPS) by subtype and phenotype.	Strong
Assess PBPS-associated non-bladder diseases systematically.	Strong
Assess PBPS-associated negative cognitive, behavioural, sexual, or emotional consequences.	Strong
Use a validated symptom and quality of life scoring instrument for initial assessment and follow-up.	Strong

4.5.4 Diagnostic evaluation of scrotal pain syndrome

Summary of evidence	LE
The nerves in the spermatic cord play an important role in scrotal pain.	2b
Ultrasound of the scrotal contents does not aid in diagnosis or treatment of scrotal pain.	2b
Post-vasectomy pain is seen in a substantial number of men undergoing vasectomy.	2b
Scrotal pain is more often noticed after laparoscopic than after open inguinal hernia repair.	1b

4.5.5 Diagnostic evaluation of urethral pain syndrome

Summary of evidence	LE
Primary urethral pain syndrome may be a part of BPS.	2a
Urethral pain involves mechanisms of neuroplasticity and neuropathic pain.	2b

4.5.6 Diagnostic evaluation of gynaecological aspects chronic pelvic pain

Summary of evidence	LE
Laparoscopy is well-tolerated and does not appear to have negative psychological effects.	1b

Recommendations	Strength rating
Take a full uro-gynaecological history in those who have had a continence or prolapse non-absorbable mesh inserted and consider specialised imaging of the mesh.	Strong
Refer to a gynaecologist following complete urological evaluation if there is a clinical suspicion of a gynaecological cause for pain. Laparoscopy should be undertaken in accordance with gynaecological guidelines.	Strong

4.5.7 Diagnostic evaluation of anorectal pain syndrome

Summary of evidence	LE
Tenderness on traction is the main criterion of the chronic anal pain syndrome.	1a

Recommendation	Strength rating
Anorectal function tests are recommended in patients with anorectal pain.	Strong

4.5.8 Diagnostic evaluation of nerves to the pelvis

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	Strength rating
Rule out confusable diseases, such as neoplastic disease, infection, trauma and spinal pathology.	Strong
If a peripheral nerve pain syndrome is suspected, refer early to an expert in the field, working within a multidisciplinary team environment.	Weak
Imaging and neurophysiology help diagnosis but image and nerve locator guided local anaesthetic injection is preferable.	Weak

4.5.9 Diagnostic evaluation of sexological aspects in chronic pelvic pain

Summary of evidence	LE
Chronic pain can lead to decline in sexual activity and satisfaction and may reduce relationship satisfaction.	2a
Men who reported having sexual, physical or emotional abuse show a higher rate of reporting symptoms of CPPPS.	2b
Sexual dysfunctions are prevalent in men with PPPS.	2b
In men with PPPS the most prevalent sexual complaints are ED and ejaculatory dysfunction.	3
In females with CPPPS all sexual function domains are lower. The most reported dysfunctions are sexual avoidance, dyspareunia and “vaginismus”.	2a
Vulvar pain syndrome is associated with PBPS.	2a
Women with PBPS 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

Recommendation	Strength rating
Screen patients presenting with symptoms suggestive for chronic primary pelvic pain syndrome for abuse, without suggesting a causal relation with the pain.	Weak

4.5.10 Diagnostic evaluation of psychological aspects of chronic pelvic pain

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	Strength rating
Assess patient psychological factors related to the pain, e.g. pain-related fear, anxiety and depressive symptoms.	Strong
Ask patients what they think is the cause of their pain and other symptoms to allow the opportunity to inform and reassure.	Strong

4.5.11 Diagnostic evaluation of pelvic floor function

Summary of evidence	LE
The ICS classification is suitable for clinical practice.	2a
Over-activity of the pelvic floor muscles is related to chronic pelvic pain, prostate, bladder and vulvar pain.	2a
Over-activity of the pelvic floor muscles is an input to the CNS 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	Strength rating
Use the International Continence Society classification on pelvic floor muscle function and dysfunction.	Strong
In patients with Chronic Primary Pelvic Pain Syndrome it is recommended to actively look for the presence of myofascial trigger points.	Weak

5. MANAGEMENT

The philosophy for the management of chronic pelvic pain is based on a bio-psychosocial model. This is a holistic approach with patients' active involvement. Single interventions rarely work in isolation and need to be considered within a broader personalised management strategy, including self-management. Pharmacological and non-pharmacological interventions should be considered with a clear understanding of the potential outcomes and endpoints. 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 [303]. 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 [304].

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 bladder pain syndrome and in many other painful and nonpainful disorders [305].

5.1.2 Physical therapy

The physiotherapist is part of the pain management team; (including doctors, psychologists and nurses). 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 [306]. The review found six RCTs, of which three showed level 1b evidence with low-risk of bias. One of these three found that Mensendieck somatocognitive therapy showed a pain reduction after one year follow-up of 64%. This approach consists of myofascial relaxation and tension, improving posture and movement in combination with cognitive behaviour therapy (CBT) [307].

Pelvic floor muscle pain

Treating pelvic floor over-activity and myofascial trigger points should be considered in the management of chronic pelvic pain. 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 chronic pelvic pain 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 body massage was carried out in patients with prostate or bladder pain. The global response rate (RR) 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 massage. Massage only improved complaints in the prostate pain group. The fact that gender distribution was different in each group is mentioned as a possible confounding factor [308]. In an RCT of 84 patients with PPPS comparing so-called conventional therapy (α-blockers, anti-inflammatory drugs and sitz baths) with biofeedback and pelvic floor muscle relaxation therapy, the authors were able to demonstrate an improvement in both groups after three months, but three months after the end of treatment, the effects only persisted in the biofeedback and pelvic floor muscle relaxation therapy patients [309].

Myofascial trigger point release

Treatment of myofascial trigger points can be done by manual therapy, dry needling and wet needling. The evidence for all the different treatments is weak, with most studies showing no significant difference between these techniques, though most studies were small and heterogeneous with regards to the patients and methods. There is no evidence that manual techniques are more effective than no treatment [310]. Most studies of dry needling have compared with wet needling. Different SRs 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 [311].

Physiotherapy in PBPS

Transvaginal manual therapy of the pelvic floor musculature (Thiele massage) in PBPS patients with high-tone dysfunction of the pelvic floor significantly improved several assessment scales [312]. The role of specific levator ani trigger point injections in women with chronic pelvic pain has been studied [313]. 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 PBPS; global response assessment (GRA) rate was 59% and 26%, respectively. Pain, urgency and frequency ratings, and symptoms 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 PBPS [314].

Primary Anal Pain Syndrome

An RCT demonstrated that biofeedback treatment was superior to electrogalvanic stimulation and massage of the Levator muscle for treating chronic primary anal pain syndrome [119]. One hundred and fifty-seven patients who had at least weekly rectal pain were investigated, but only patients with tenderness on traction of the pelvic floor showed a significant treatment benefit. In patients with tenderness of the puborectalis muscle (Rome II: "Highly likely Levator Ani Syndrome"), 87% reported adequate relief after one month of biofeedback vs. 45% for electrogalvanic stimulation, and 22% for massage. These results were maintained at twelve months with adequate relief after nine sessions of biofeedback in 58% of the whole group (Rome II: "Highly likely" and "Possible Levator Ani Syndrome"), after galvanic stimulation in 27% and massage in 21% of patients. As previously described in dyssynergic defecation, the ability to expel a 50 mL water filled balloon and to relax pelvic floor muscles after biofeedback treatment were predictive of a favourable therapeutic outcome [119]. The pathophysiology of the chronic primary 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 chronic pelvic pain

Couples often benefit from early referral for relationship and sexual counselling during their treatment course [315]. It needs to be remembered that sexual difficulties will arise as a result of pelvic pain syndromes as well as those disorders potentially being primary. 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 the activity to less than that which causes pain. Planning for the time of intercourse is important, and scheduling a clinic visit after intercourse might be useful to identify specific sites and causes of post-coital flares. The corresponding evidence in men is lacking, but similar principles would apply. Other behavioural changes involve pre- and post-coital voiding, application of ice packs to the genital or suprapubic area [315, 316], and increased use of vaginal dilators, fingers or sex toys. Lubricants can also be used and women with signs of vulvovaginal atrophy may benefit from oestrogen cream [317]. Optimising the pelvic floor muscle is indicated when dysfunction is present and will relieve the pain [318-320].

Other physical therapy interventions

Electromagnetic therapy. A small, sham-controlled, double-blind study of four weeks showed a significant, sustained effect over a one-year period for CPPPS [321].

Microwave thermotherapy. In uncontrolled studies significant symptomatic improvement has been reported from heat therapy, for example, transrectal and transurethral thermotherapy [322, 323].

Extracorporeal shockwave therapy. A small sham-controlled double-blind study of four times weekly perineal extracorporeal shockwave therapy (n=30) in men with CPPPS showed significant improvement in pain, QoL, and voiding compared to the control group (n=30), over twelve weeks [324]. Two other randomised sham-controlled studies, have been published more recently, one comparing ten treatment sessions over two weeks (n=40 vs. n=40) [325], another with four times weekly treatments (n=20 vs. n=20) [326]. Both concluded there was a significant effect in terms of total NIH-CPSI score and pain at twelve weeks. Unfortunately, no long term effects at 24 weeks could be shown in a published follow-up study of the second [327]. A Cochrane review of non-pharmacological interventions for chronic pelvic pain reported a reduction in symptoms following treatment compared with control and concluded that extracorporeal shockwave therapy may improve symptoms without an increase in adverse events [328]. In addition, a recent SR and meta-analysis concluded that extracorporeal shockwave therapy is effective for the improvement of pain and quality of life, but longterm efficacy was non-significant [329]. Publications show a potential role for external shock wave lithotripsy applied to the bladder. In an RCT enrolling 54 patients, improvement in the VAS > 3 was 57.1% vs. 19.0% (ESWT vs. placebo; P =.011), at 12 weeks post treatment. However, the primary endpoint did not reach significance [330].

Acupuncture. An RCT comparing acupuncture (n=50) vs. shamcontrolled (n=50), once weekly treatment for six weeks showed significant long lasting improvement at 24 weeks in terms of RR and overall symptom scores [331]. Another RCT showed a significant effect for a follow-up of 32 weeks [332]. Two SRs and meta-analyses were published in 2016 analysing seven RCTs on a total of 471 participants comparing acupuncture to sham control or oral medical treatment [333, 334]. Both came to the conclusion that acupuncture was effective and safe, significantly reducing total NIH-CPSI scores compared to sham or medical treatment, and should be considered as a treatment option. This is in line with the conclusion of a Cochrane review [328] on non-pharmacological treatment options. In a large multicentre RCT comparing acupuncture (N=220) with sham acupuncture (N=220) in patients with PPPS over a period of 8 weeks (20 sessions), the authors could show a superior improvement of symptoms in the acupuncture group with durable effects 24 weeks after treatment [335]. In a more recently published SR and meta-analysis of only high quality trials (JADAD score >=4), the authors concluded that acupuncture compared to sham acupuncture was superior in terms of pain score, NIH-

CPSI score, quality of life score, urinary symptom, and efficacy rate [336].
Posterior tibial nerve stimulation. See section 5.3.2, Neuromodulation.
Transcutaneous electrical nerve stimulation. See section 5.3.2, Neuromodulation.

5.1.3 Psychological therapy

Psychological interventions may be directed at pain itself or at adjustment to pain in terms of function and mood and reduced health-care use, with or without pain reduction. Ideally, treatment follows general principles and practice in the field of chronic pain [337, 338] but these have been neglected in pelvic pain. Three SRs and meta-analyses of the few heterogeneous trials of psychologically based treatment for pelvic pain [339-341] found benefits for pain comparable to those from pharmacotherapy over a few months, but this was not sustained at follow-up. Exposure to pain-related fears in women with chronic pelvic pain proved superior to manual therapy in reducing those fears and overall pain disability, albeit assessed only by self-report [342]. The importance of multi-disciplinary treatment is emphasised by several reviews [44, 343, 344] of intervention for diverse chronic pains, but standard multi-component psychologically-based programmes for pelvic pains are mostly in the pilot stages [345], with mixed findings so far [346]. For primary focal vulvar pain syndrome, multimodal physiotherapy integrating psychological components has shown beneficial effects, although more research on the effects of psychological therapy and multi-component psychologically-based programmes is needed in this patient group [347]. For less disabled and distressed patients treatment can be delivered remotely [348, 349].

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 primary pelvic pain syndrome

In this section the evidence available for specific CPPPSs is presented. Where there is no evidence the reader is directed to the section on analgesics below (Section 5.2.2) 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 PPPS, one reason for treatment failure in some large placebo-controlled RCTs, may be the heterogeneity of the patient population [350]. One strategy for improving treatment effects may be stratification of patient phenotypes. A prospective series of phenotypically directed treatment for CPPPS has shown significant improvement of symptoms and QoL [351]. Monotherapeutic strategies for the treatment of CPPPS may fail [352], therefore, most patients require multimodal treatment aimed at the main symptoms, and taking comorbidity into account. In the past ten years, results from RCTs have led to advances in standard and novel treatment options.

5.2.1.1 Mechanisms of action

Mechanisms of action are discussed as appropriate under the drugs headings below.

5.2.1.2 Comparisons of agents used in pelvic pain syndromes

Primary Prostate Pain Syndrome (PPPS)

Anti-inflammatory drugs

For non-steroidal anti-inflammatory agents (NSAIDs), a trial with celecoxib reported that the pain sub-score, QoL sub-score, and total NIH-CPSI score were in favour of the treatment arm vs. placebo, but effects were limited to the duration of therapy [353]. In a meta-analysis, two studies of NSAIDs [259, 353] and one with prednisolone [354] were pooled. Anti-inflammatory drugs were 80% more likely to have a favourable response than placebo. In 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. A Cochrane SR from 2019 concluded that anti-inflammatories may reduce prostatitis symptoms compared to placebo [355]. Overall, a moderate treatment effect has been shown for anti-inflammatory drugs, but larger studies are needed for confirmation, and long-term side-effects have to be taken into account.

α-blockers

Positive results from RCTs of α-blockers, i.e. terazosin [356, 357], alfuzosin [358], doxazosin [359, 360], tamsulosin [361, 362], and silodosin [363] have led to widespread use of α-antagonists in the treatment of PPPS in recent years. Whereas one SR and meta-analysis has not reported a relevant effect of α-blockers due to study heterogeneity [364], another network meta-analysis of α-blockers [363] has shown significant improvement in total symptoms, pain, voiding, and QoL scores. In addition, they had a higher rate of favourable response compared to placebo [relative risk (RR): 1.4; 95% 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, α-blockers seem to have moderate but significant beneficial effects. This probably is not the case for long-standing PPPS patients [365]. A Cochrane Systematic review published in 2019 reported an uncertain treatment effect of α-blockers on "prostatitis" symptoms, and little to no difference in sexual dysfunction, quality of life, anxiety and depression [355]. Future studies should show if longer duration of therapy or some sort of phenotypically directed (e.g., patients with PPPS and relevant voiding dysfunction) treatment strategies will improve treatment outcomes.

Antibiotic therapy

Empirical antibiotic therapy is widely used because some patients have improved with antimicrobial therapy. Patients responding to antibiotics should be maintained on medication for four to six weeks or even longer. Unfortunately, culture, leukocyte and antibody status of prostate-specific specimens do not predict antibiotic response in patients with PPS [366], and prostate biopsy culture findings do not differ from those of healthy controls [367]. The only placebo-controlled RCTs of sufficient quality have been done for oral antibiotic treatment with ciprofloxacin (six weeks) [368], levofloxacin (six weeks) [369], and tetracycline hydrochloride (twelve weeks) [370]. The studies have been analysed in meta-analyses [363, 371]. Although direct meta-analysis has not shown significant differences in outcome measures, network meta-analysis has suggested significant effects in decreasing total symptom, pain, voiding, and QoL scores compared with placebo. Combination therapy of antibiotics with α-blockers has shown even better outcomes in network meta-analysis. Despite significant improvement in symptom scores, antibiotic therapy did not lead to statistically significant higher response rates [371]. In addition, the sample sizes of the studies were relatively small and treatment effects only modest, mostly below clinical significance. It may be speculated that patients profiting from treatment had some unrecognised uropathogens. A Cochrane SR reported that antibiotics may reduce "prostatitis" symptoms compared to placebo [355]. If antibiotics are used, other therapeutic options should be offered after one unsuccessful course of a quinolone or tetracycline antibiotic over six weeks. In addition, it is very important that unnecessary antibiotic use is avoided and local resistance patterns are considered. In this regard, the relevant recommendations of the EAU Guidelines on Urological Infections should be followed [372].

5-α-reductase inhibitors

Although a few small pilot studies with 5-α-reductase inhibitors supported the view that finasteride may improve voiding and pain, the first RCT published in a peer-reviewed journal did not support this, although the study lacked power [373]. In another RCT, finasteride provided better amelioration of symptoms compared to saw palmetto over a one-year period, but lacked a placebo-control arm [374]. A six-month placebo-controlled study showed a non-significant tendency towards better outcome in favour of finasteride, possibly because of a lack of statistical power [362]. A Cochrane review concluded that finasteride probably reduces prostatitis symptoms compared to placebo [355]. The NIH-CPSI scores decreased significantly in a subgroup of men enrolled in a prostate cancer risk reduction study treated with dutasteride compared to placebo [363]. Patients (n=427, age 50 to 75, with elevated prostate-specific antigen [PSA]) were included if they had significant "prostatitis like" symptoms at baseline. Based on the evidence, 5-α-reductase inhibitors cannot be recommended for use in PPPS in general, but symptom scores may be reduced in a restricted group of older men with an elevated PSA [363].

Phytotherapy

Phytotherapy applies scientific research to the practice of herbal medicine. An adequately powered placebocontrolled RCT of a pollen extract (Cernilton) showed clinically significant symptom improvement over a twelve week period in inflammatory PPPS patients (NIH Cat. IIIA) [375]. The effect was mainly based on a significant effect on pain. Another pollen extract (DEPROX 500) has been shown to significantly improve total symptoms, pain and QoL compared to ibuprofen [376]. In an RCT of patients treated with pollen extract suppositories (n=70) vs. oral ibupofen (n=71) over a period of ten days, the authors could find a clinically significant effect up to six months of follow-up including fewer adverse events in the pollen extract group [377]. A SR and meta-analysis of pollen extract for the treatment of PPPS showed significant improvement in overall QoL [378]. As an adjunct to α-blocker therapy, cernitin pollen extract proved superior to tadalafil in terms of pelvic pain and discomfort [379]. Quercetin, a polyphenolic bioflavonoid with documented antioxidant and anti-inflammatory properties, improved NIH-CPSI scores significantly in a small RCT [380]. In a large multicentre

trial of 221 patients over twelve weeks, saw palmetto extract (Serenoa repens) led to statistically significant improvement in the NIH-CPSI total score and sub-scores compared to placebo [381]. In a SR and meta-analysis, patients treated with phytotherapy were found to have significantly lower pain scores than those treated with placebo [363]. In addition, overall RR in network meta-analysis was in favour of phytotherapy (RR: 1.6; 95% CI: 1.1-1.6).

Pregabalin is an anti-epileptic drug that has been approved for use in neuropathic pain. In an adequately powered placebo-controlled RCT, which was the only report included in a published Cochrane review [382], a six-week course of pregabalin (n=218) compared to placebo (n=106) did not result in a significant reduction of NIH-CPSI total score [383]. This group thinks it may have a role in selected patients and should be used in accordance with the paragraph 5.2.22

Pentosane polysulphate is a semi-synthetic drug manufactured from beech-wood hemicellulose. One study using oral high-dose (3 x 300 mg/day) demonstrated a significant improvement in clinical global assessment and QoL over placebo in men with PPPS, suggesting a possible common aetiology [384].

Muscle relaxants (diazepam, baclofen) are claimed to be helpful in sphincter dysfunction or pelvic floor/perineal muscle spasm, but there have been few prospective clinical trials to support these claims. In one RCT, a triple combination of a muscle relaxant (thiocolchicoside), an anti-inflammatory drug (ibuprofen) and an α-blocker (doxazosin) was effective in treatment-naïve patients, but not superior to an α-blocker alone [360].

Botulinum toxin type A (BTX-A) for the treatment of CPPPS is an off-label use, but a recent SR identified two RCTs and one non-randomised comparative study assessing intraprostatic BTX-A injections (100-200 units) for treatment of PPPS [385]. All three papers used the NIH-CPSI to score pain. Although two of the studies reported a statistically significant reduction in pain, incomplete data and differences in dose and study methodology precluded calculation of a summary effect estimate for BTX-A-related improvement in pain. No definitive conclusions could be drawn from the review.

Zafirlukast, a leukotriene antagonist, and prednisone in two low-power placebo-controlled studies failed to show a benefit [354, 386]. More recently, a placebo-controlled phase II a study of tanezumab, a humanised monoclonal antibody that specifically inhibits the pain mediating neurotrophin, nerve growth factor, failed to demonstrate significant effect [387] and should only be used in clinical trials.

Allopurinol
There is insufficient evidence for the use of allopurinol in PPPS [388, 389].

Primary Bladder Pain Syndrome (PBPS)

Treatments of significant value for PBPS

Anti-histamines
Mast cells may play a role in PBPS. Histamine is one of the substances released by mast cells. Histamine receptor antagonists have been used to block the H1 and H2 receptor subtypes, with variable results. A prospective placebo-controlled RCT of hydroxyzine or oral pentosane polysulphate did not show a significant effect [390].

Amitriptyline
Amitriptyline is a tricyclic antidepressant. Several reports have indicated improvement of PBPS symptoms after oral amitriptyline. Amitriptyline has been shown to be beneficial when compared with placebo plus behavioural modification [391]. Drowsiness is a limiting factor with amitriptyline, nortriptyline is sometimes considered instead.

Pentosane polysulphate
Pentosan polysulphate is a semi-synthetic drug manufactured from beech-wood hemicellulose. Subjective improvement of pain, urgency, frequency, but not nocturia, has been reported [392, 393]. Pentosane polysulphate had a more favourable effect in PBPS type 3 C than in non-lesion disease [394]. Response was not dose dependent but related more to treatment duration. At 32 weeks, about half the patients responded. Combination therapy showed a RR of 40% compared to 13% with placebo. For patients with an initial minor response to pentosane polysulphate, additional subcutaneous heparin was helpful [395, 396].

Immunosuppressants
Azathioprine treatment has resulted in disappearance of pain and urinary frequency [397]. Initial evaluation of methotrexate [398] showed good analgesic effect but limited efficacy for urgency and frequency. Corticosteroids are not recommended in the management of patients with PBPS because of a lack of evidence.

Intravesical Treatments
Intravesical drugs are administered due to poor oral bio-availability establishing high drug concentrations within the bladder, with few systemic side-effects. Disadvantages include the need for intermittent catheterisation which can be painful in PBPS patients, cost and risk of infection.

- **Local anaesthetics**

There are sporadic reports of successful treatment of PBPS with intravesical lidocaine [399, 400]. Alkalisation of lidocaine improves its pharmacokinetics [401]. Combination of heparin, lidocaine and sodium bicarbonate gave immediate symptom relief in 94% of patients and sustained relief after two weeks in 80% [402]. Intravesical instillation of alkalised lidocaine or placebo for five consecutive days resulted in significantly sustained symptom relief for up to one month [403].

- **Hyaluronic acid and chondroitin sulphate**

These are described to repair defects in the GAG layer. Despite the fact that intravesical GAG replenishment has been in use for about twenty years for PBPS/IC, most of the studies are uncontrolled and with a small number of patients. Based on the studies available there are differences by virtue of substance classes, whether they are natural GAG layer components, dosage formulations, or concentrations. An RCT seems to reinforce the case for GAG layer replenishment, however it lacks a placebo arm [404]. A meta-analysis confirms usefulness of GAG layer replenishment [412]. However, most retrieved studies are non-randomised and with scarce numbers.

- **Intravesical heparin**

Primary bladder pain syndrome patients were treated with heparin for three months, and over half had control of symptoms, with continued improvement after one year of therapy [405]. Intravesical heparin plus peripheral neuromodulation in patients with refractory PBPS was studied and it was shown that voiding frequency, pain score and maximum cystometric capacity were significantly better after two and twelve months [406].

- **Hyperbaric oxygen**

This has a moderate effect on a small subgroup of PBPS patients. Disadvantages include high cost, limited availability of treatment sites, and time-consuming treatment [395].

<u>Treatments of limited value for PBPS</u>

Cimetidine
There are limited data to suggest that cimetidine improves symptoms of PBPS in the short-term. Compared with placebo for three months, cimetidine significantly improved symptom scores, pain and nocturia, although the bladder mucosa showed no histological changes in either group [407].

Prostaglandins
Misoprostol is a prostaglandin that regulates various immunological cascades. After three months of treatment with misoprostol, fourteen out of 25 patients had significantly improved, with twelve showing a sustained response after a further six months [408]. The incidence of adverse drug effects was 64%.

L-Arginine
Oral treatment with the nitric oxide (NO) synthase substrate L-arginine was suggested to decrease PBPS-related symptoms. However, no symptomatic relief or change in NO production could be shown after treatment [409, 410].

Oxybutynin is an anti-cholinergic drug used in overactive detrusor dysfunction. Intravesical oxybutynin combined with bladder training improves functional bladder capacity, volume at first sensation, and cystometric bladder capacity [411]. However, an effect on pain has not been reported.

Duloxetine (a serotonin-noradrenaline re-uptake inhibitor antidepressant with a licence for the management of neuropathic pain) did not significantly improve symptoms of PBPS [412]. Administration was safe. Based on these preliminary data, duloxetine cannot be recommended for treatment of PBPS.

PDE5 inhibitors are drugs currently used for erectile dysfunction. In different RCT improved all parameters evaluated at twelve weeks, but at 24 weeks results were not consistent for pain VAS score [413]. Using a PDE5i, theoretically, the activation of C fiber is decreased, bladder afferent activity is reduced and detrusor muscle tone relaxes.

Primary Scrotal Pain Syndrome (PSPS)

Treatment of primary scrotal pain syndrome is based on the principles of treating chronic pain syndromes, as described throughout these guidelines.

In men with pain post inguinal hernia repair, there is limited evidence from case series showing that neurectomy of the damaged nerves can lead to symptomatic benefit [185, 414].

For scrotal pain post vasectomy, affected men may find that reversal of vasectomy can cure symptoms especially in those in whom patency is achieved [415]. In a prospective RCT, pulsed radio-frequency to the ilioinguinal and genitofemoral nerves is associated with high rates of symptomatic improvement (80%) but follow up was limited to three months [416]. The evidence for epididymectomy is poor but if considered, is less likely to provide benefit if the epididymis has a normal sonographic appearance [417].

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 chronic pelvic pain is unrelated to any of the well-defined conditions, it is often difficult to determine a therapeutic pathway other than a multidisciplinary chronic abdomino-pelvic pain management plan. A Cochrane review suggests there may be some evidence (moderate) supporting the use of progestogens [340]. Though efficacious, physicians need to be knowledgeable of progestogenic side effects (e.g., weight gain, bloatedness - the most common adverse effects) which can stop some patients from accepting such medication. Gonadotropin-releasing hormone (GnRH), such as goserelin, are also thought to help such pain. However, when compared with progestogens, their efficacy remains limited. The quality of evidence is generally low and drawn from single studies [340]. Gonadotropin-releasing hormone on the other hand binds to specific receptors on pituitary gonadotrophs, leading to desensitisation and consequently to suppressed gonadotropin secretion. By contrast, GnRH antagonists compete with GnRH for receptors thus gonadotrophin secretion, which may be beneficial in certain clinical applications, such as reducing the size of fibroids, endometrial bleeding and endometriosis [418].

Pelvic Floor, Abdominal and Chronic Anal Pain

Botulinum toxin type A (pelvic floor)

Pelvic floor muscle over-activity plays a role in CPPPS. Botulinum toxin type A, as a muscle relaxant, can be used to reduce the resting pressure of the pelvic floor muscles and injection of the puborectalis and pubococcygeus muscles has been used to treat spasm of the levator ani A pilot study of twelve women with pelvic floor muscle overactivity as defined by a vaginal resting pressure > 40 cm H2O on vaginal manometry reported a reduction in resting pressure with improvement in dyspareunia and dysmenorrhoea, but no significant changes in non-menstrual pelvic pain scores [419]. A SR including three RCTs comparing BTX-A with saline injections into the pelvic floor found no benefit in pain scores at six months follow-up despite a reduction in pelvic floor pressure [385].

Botulinum toxin type A has been injected into trigger points. It is more expensive than lidocaine and has not been proven to be more effective [420]. Reviews do not support the injection of BTX-A into trigger points [421].

Botulinum toxin type A can also be injected at the sphincter level to improve urination or defecation. Relaxation of the urethral sphincter alleviates bladder problems and secondarily the spasm. In a cohort study of thirteen patients with CPPPS, BTX-A was injected into the external urethral sphincter. Subjectively, eleven patients reported a substantial change in pain symptoms, from a score of 7.2 to 1.6 on a VAS [422].

Intermittent chronic primary anal pain syndrome

Due to the short duration of the episodes, medical treatment and prevention is often not feasible. Inhaled β-2 adrenergic agonist salbutamol was effective in an RCT in patients with frequent symptoms and shortened pain duration [423]. Other treatment options are topic diltiazem and BTX-A [424]. However, there is still some controversy regarding the duration of pain of intermittent chronic and chronic primary anal pain syndrome. Randomised controlled trials often use different definitions, extending the pain duration (with a shift to chronic pain) in order to include more patients and to better evaluate the study-drug action.

Abdominal pain associated with Irritable Bowel Syndrome

Linaclotide, a minimally absorbed peptide guanylate cyclase-C agonist at a dose of 290 µg once daily significantly improved abdominal pain (48.9% vs. 34.5% placebo-treated) and bowel symptoms associated with IBS with constipation over 26 weeks of treatment [425]. Diarrhoea was the most common adverse event in patients treated with linaclotide (4.5%). Although it is known to overlap with IBS pelvic pain, effect on the latter was not assessed in this study.

In a Cochrane Meta-analysis antispasmodics had a beneficial effect for improvement of abdominal pain compared to placebo (58% improved on antispasmodic compared to 46% on placebo) in IBS [426]. Peppermint oil showed in a meta-analysis of nine RCT's improvement in abdominal pain in patients with IBS [427].

*5.2.2 **Analgesics***

If the use of simple analgesics fails to provide adequate benefit, then consider using neuropathic agents, and if there is no improvement, consider involving a specialist pain management centre with an interest in pelvic pain. Chronic pelvic pain is well defined and involves multiple mechanisms as described in previous sections.

The management requires a holistic approach with biological, psychological and social components. Few studies have specifically looked at medications used in CPPPS [428], therefore, a wider look at the literature has been undertaken and further specific research is required. The agents concerned are divided for ease of description. Combinations often provide a greater benefit than individual agents [429]. They may also allow lower individual dosages and thus minimise side-effects. The aim of using these drugs is to allow patients to improve their QoL. This is best measured by assessing their function as well as pain severity. If the use of these agents does not allow this, then they should be withdrawn. Unfortunately, the failure of one agent does not exclude potential benefit of an alternative. If the benefit is limited by side-effects, then the lowest effective dose should be found (by dose titration). Sometimes, patients will prefer a higher level of pain and have fewer side effects.

5.2.2.1 Mechanisms of action

Mechanisms of action are discussed as appropriate under the drug headings below.

5.2.2.2 Comparisons within and between groups in terms of efficacy and safety

Paracetamol (acetaminophen)

Paracetamol is a well-tolerated analgesic in a class of its own. This is an antipyretic analgesic with a central mechanism of action [430]. It is often available over the counter without prescription. A review questions its routine use as a first-line analgesic based on inadequate evidence of efficacy in many pain conditions including dysmenorrhoea [431]. It will not be effective for all patients and individual responses should be reviewed when deciding on longer term use.

Non-steroidal anti-inflammatory agents

These agents are anti-inflammatory, antipyretic analgesics that act by inhibiting the enzyme cyclooxygenase (COX). They have a peripheral effect, hence their use in conditions involving peripheral or inflammatory mechanisms. They are commonly used for pelvic pain; many are available over the counter and are usually well-tolerated. There is insufficient 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 chronic pelvic pain is weak or non-existent and is often limited by side-effects. For pelvic pain in which inflammatory processes are considered important, such as dysmenorrhoea [432], 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 [433] 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 agents 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 and all have side-effects that may limit their use and have the potential to be dependence-forming. In the UK, NICE has reviewed the pharmacological management of neuropathic pain [434]. The evidence for treatment of CPPPS 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. Early identification of neuropathic pain with a simple questionnaire could facilitate targeted therapy with neuromodulators [58].

Antidepressants

Tricyclic antidepressants

The tricyclic antidepressants (TCAs) have multiple mechanisms of action and are frequently limited by their side-effects. Tricyclic antidepressants have a long history of use in pain medicine and have been subjected to a Cochrane review [435], suggesting that they are effective for neuropathic pain. Amitriptyline is the most commonly used at doses from 10-75 mg/day (sometimes rising to 150 mg/day). This is titrated against benefit or side-effects and should be taken at night [434]. Nortriptyline and imipramine are used as alternatives.

Other Antidepressants

Duloxetine is a SNRI antidepressant licensed for use in depression, SUI and neuropathic pain. There is evidence of benefit in diabetic neuropathy and fibromyalgia at a dose of 60 mg/day [436, 437]. Side-effects are common and may result in its discontinuation.

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 Pain Guidelines [434].

Carbamazepine has a long history of use in neuropathic pain. Evidence exists for its benefit [438]. Trials trend 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.

Gabapentinoids

There is a growing awareness and evidence of the risk for dependence and misuse of gabapentinoids [439]. A formal assessment of efficacy against benefit and side-effects (both pain and QoL) is required with the patient in order to determine the lowest effective dose and if longer-term treatment is to be used.

Gabapentin is commonly used for neuropathic pain and has been systematically reviewed [440, 441]. This demonstrates good evidence for postherpetic neuralgia and diabetic neuropathy but evidence for other neuropathies is limited. A double-blind RCT looking at CPPPS in women with no obvious pathology demonstrated no benefits but higher levels of side effect [441].

Pregabalin is a commonly used neuromodulator with good evidence of efficacy in some neuropathic conditions [442]. The dose for benefit is in the range of 300-600 mg/day. Evidence for central neuropathic pains is inadequate. Some patients do gain moderate to significant benefit but most will gain no benefit and then the drug should be discontinued. Other agents can be used in the management of neuropathic pain but they are best administered by specialists in the management of pain whom are 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 multi-dimensional management plan.

Opioids

Over recent years opioids have been used extensively for managing chronic non-cancer pain. There is increasing evidence that their role is limited in this population, but may be beneficial for a small number of patients at a low dose in a managed setting [443]. There is clear evidence of harm and significant professional, public and political interest. Their use is beneficial for both acute pain and for cancer pain management particularly towards the end of life.

Often patients will stop taking oral opioids due to side effects or insufficient analgesic effect [444]. There is clear evidence of harm including effects on the endocrine and immune systems as well as a growing understanding of opioid-induced hyperalgesia [445]. There is limited guidance on the best method for tapering the dose of opioids with the aim of stopping or finding the lowest effective dose [446].

Opioids 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. Ensure there are arrangements for formal monitoring, follow-up and review. If opioids are used and the pain remains, then they are not working and should be stopped even if there is no alternative [445].

The risk of harm increases substantially at doses above 120 mg/day morphine equivalence [445] and guidance suggests regular (at least annual) review for patients with over 50 mg/day morphine equivalence and pain specialist involvement above 90 mg/day morphine equivalence [447].

There are well-established guidelines for the use of opioids in pain management as well as considering the potential risks [445, 447]. Opioid reduction and optimisation should be undertaken where opioids are not providing clear measurable benefit. There is also information available online for patients [445]. Opioids Aware is a web-based resource for patients and healthcare professionals, jointly produced by the Faculty of Pain Medicine of Royal College of Anaesthetists and Public Health England, to support prescribing of opioid medicines for pain. https://fpm.ac.uk/opioids-aware.

Cannabinoids

There has been increasing interest and changes in national regulations regarding the use of cannabinoids for medicinal use. Regarding pain the evidence base for the use of cannabinoids is weak [448-450] and further well conducted clinical trials are necessary. This is an area where further guidance and research is likely in the coming years.

5.3 Further management

5.3.1 ***Nerve blocks***

Nerve blocks for pain management are usually carried out by specialists in pain medicine as part of a broader management plan [451]. 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 [452].

Pudendal Neuralgia

The role of injections may be divided into two. First, an injection of local anaesthetic with or without steroids at the sight of nerve injury or nerve entrapment may produce a therapeutic action [453, 454]. 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 [250, 455-457].

Infiltration at the ischial spine requires the use of a nerve stimulator/locator. Both motor (anal contraction) and sensory endpoints may be noted. The anatomical endpoint may be localised by fluoroscopy, CT guidance, or the use of US, the latter avoids any radiation, whereas CT guidance involves a significant amount of radiation. Fluoroscopy and ultrasound guidance imaging are the most frequently used techniques for performing nerve block because it is readily available to most anaesthetists. Pulsed radio frequency lesioning for pudendal neuralgia is being developed with a paper demonstrating potential benefit. Follow-up is short term and further research is required to better elucidate its place in management [458].

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 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, sacral root stimulation, dorsal root ganglion stimulation or peripheral nerve stimulation). These are expensive interventional techniques for patients refractory to other therapies. Neuromodulation is still finding its role in pelvic pain

management. There has been growing evidence but more detailed, high quality research is required [459]. Its role in overactive bladder (OAB) and faecal incontinence is more robust but is limited for pain. Two SRs have evaluated neuromodulation techniques for CPPS [460, 461]. Both studies concluded that neuromodulation may be effective in reducing pain and improving QoL in patients with CPPS; however, studies were of a low quality and long-term results were needed.

Transcutaneous Electrical Nerve Stimulation

Transcutaneous electrical nerve stimulation (TENS) is a non-invasive technique used in many pain conditions. A SR identified twelve studies of TENS in chronic pelvic pain conditions including four RCTs [460]. All RCTs demonstrated a significant reduction in pain following twelve weeks of treatment for pain conditions including dysmenorrhoea and CPPPS. Pain was also found to improve following TENS for provoked vestibular pain. There was conflicting data with regard to improvement of QoL following TENS; where validated questionnaires were used, no significant improvement was found, whereas in trialist-defined studies, an improvement was seen in TENS for dysmenorrhea and CPPPS. The beneficial effects of a course of TENS may be sustained; one study demonstrating a persistent benefit at 43 months in 73% of men with CPPPS and another demonstrating a prolonged significant improvement in women with provoked vestibular pain at ten months post-treatment. Where reported there were no adverse events recorded. Transcutaneous electrical nerve stimulation could offer an effective non-invasive treatment option for patients with CPPPS.

Percutaneous Tibial Nerve Stimulation

Percutaneous tibial nerve stimulation (PTNS) is a minimally invasive technique that can be use in an outpatient setting. Two SRs have shown that PTNS is effective in reducing pain in patients with CPPPS [460, 461]. Three RCTs identified showed a significant improvement in pain scores and QoL as measured by validated questionnaires. Where recorded, adverse events were rare and minor including temporary slight pain at application site and haematoma.

Sacral Nerve Stimulation

Sacral nerve stimulation (SNS) is an invasive technique requiring sedation or general anaesthesia for implantation of a device following trial stimulation. A SR review identified ten studies of SNS in CPPPS, either retrospective case series or prospective cohort studies and no RCTs. Where reported, a mean of 69% of participants progressed to implantation of device following test stimulation (range 52-91%). All studies reported an improvement in pain, statistically significant in five studies. Quality of Life was measured in three studies and a significant improvement demonstrated in two of three studies. There was a large variation in adverse events reported ranging from 0-50%. Complications not requiring surgical intervention included pain, failure of device, wound infection and seroma. Re-operation rate ranged between 11-50% for complications including lead migration, systemic infection, intrathecal implantation, loss of efficacy and erosion. In clinical practice, a patient should be appropriately counselled regarding the need for a period of trial stimulation and whilst there may be an improvement in symptoms, this should be weighed against a notable complication rate.

A SR review in 2018 identified fourteen studies. In all, 403 patients had undergone percutaneous nerve evaluation and/or SNM stage 1 and 54.8%) had progressed to the permanent implantation stage, which is similar to that reported previously. The cause of pain was reported to be IC/BPS in 170 cases (42.2%). Visual Analogue Scale pain scores were available pre- and post-SNM in 210 patients and overall improvement in pain scores was significant. Sacral nerve stimulation is a promising treatment option for refractory chronic pelvic pain. This is mainly supported by level 2b studies. Randomised prospective studies are warranted to compare SNS vs. other modalities for chronic pelvic pain treatment. Further studies are needed to compare antegrade vs. retrograde approaches [462].

Other neuromodulation techniques

A variety of other techniques of neuromodulation for patients with CPPPS were identified by SRs [460, 463]. These techniques include intravaginal electrical stimulation for women with CPPPS, pudendal nerve stimulation for CPPPS, spinal cord stimulation for pudendal neuralgia, transcutaneous interferential electrical stimulation for IBS, electrical acupuncture for dysmenorrhoea and electrical stimulation/biofeedback and electromagnetic stimulation for men with CPPPS. Whilst an improvement in pain has been reported in these studies, it is noted that they are largely of low quality and further work is needed in this area to enable robust clinical recommendations to be made. Neuromodulation in combination with hormonal treatment in deep endometriosis may have some benefit [464].

*5.3.3 **Surgery***

Primary Bladder Pain Syndrome (PBPS)

Bladder distension
Although bladder hydrodistension is a common treatment for PBPS, the scientific justification is scarce. It can be part of the diagnostic evaluation, but has limited therapeutic role [465].

Hydrodistension and Botulinum toxin type A
Botulinum toxin type A may have an anti-nociceptive effect on bladder afferent pathways, producing symptomatic and urodynamic improvements [466]. Treatment with hydrodistension and hydrodistension plus intravesical BTX-A has been compared [467]. There was symptomatic improvement in all patients. However, in the hydrodistension-only group, 70% returned to their previous symptoms after one month, while in the BTX-A-treated patients, VAS score and functional and cystometric bladder capacity improved at three months. Botulinum toxin type A trigonal-only injection seems effective and long-lasting as 87% of patients reported improvement after three months follow-up [468]. Over 50% reported continued benefit nine months after the first treatment. When re-treatment was needed, similar results were obtained. Up to 59% of patients remain responders after 9 treatments. The sustained duration of the effect, despite the increase in the number of procedures, suggests that intratrigonal sensory neurons do not develop tolerance to OnaBotA, even during long periods of administration [469]. Adverse effects of BTX-A administration for IC/PBPS were significantly less than for OAB syndrome, namely in increased postvoid residual volumes and decreased voiding efficiency [470]. Recent RCTs have reported benefits and long efficacy of BTX-A administration [471-474], but a summary estimate for overall change in pain following BTX-A injections was not possible in a recent SR [385]. Conflicting data on results hinders issuance of a clear guideline for the use of Botox in PBPS phenetypes [475].

Results of treatment with intravesical plasma rich (PRP) injections are also being explored. A recent prospective trial, showed that patients with GRA (global response assessment) > 2, had success rates at one month and at three months after the fourth PRP injection, of 70.6% and 76.7%, respectively. The VAS pain score, frequency, and nocturia showed a significant decrease (all $p < 0.05$). However, further studies are needed to validate findings [476].

Transurethral resection, coagulation and laser ablation
Endourological destruction of bladder tissue aims to eliminate urothelial Hunner lesions. Coagulation of glomerulations or petequiae area is not recommended. Since the 1970s, resection and fulguration have been reported to achieve symptom relief, often for more than three years [477-479]. Repeated resection or fulguration treatments should be wisely indicated. A more recent study has shown no difference in therapeutic benefit between transurethral laser ablation or resection [479].

Major Surgery for PBPS [480]
Primary bladder pain syndrome is a benign condition that can severely impact quality of life but does not shorten life expectancy. Consequently major operative procedures are ranked last in the therapeutic algorithm and are only appropriate as a last resort for patients with severe refractory disease. The level of evidence underpinning reconstructive surgery is weak with no consensus regarding the optimal surgical approach. A systematic review with 450 patients (90% female, median age 54.5 years) from 20 eligible studies reported symptomatic improvement in 77.2% of patients with an overall complication rate of 26.5% and a mortality of 1.3% [480]. This complication rate is likely to be an underestimate as a third of the procedures did not specify their complication data. All the studies included the systematic review were retrospective and observational with no control groups. There was also heterogeneity in the diagnostic criteria and outcome measures used. The main surgical options performed comprised:

1. Urinary diversion without cystectomy is performed to minimise the duration and complexity of surgery and preserve sexual function and fertility, but complications related to the retained bladder commonly occur with the incidence of pyocystis reported to range between 3.3% and 67%.

2. Subtotal (supratrigonal) cystectomy with substitution cystoplasty is the preferred reconstructive approach particularly in younger patients [481] and the use of various intestinal segments has been reported [482-484].

3. Total (subtrigonal) cystectomy and orthotopic neobladder formation has the benefit of removing the trigone as a possible disease site, but requires ureteric re-implantation. Trigonal disease is reported in 50% of patients and surgical failure has been blamed on the trigone being left in place [485], especially in patients with non-lesion type disease [486, 487]. Incomplete emptying of the orthotopic bladder augmentation is most likely to occur following trigonal resection so intermittent self-catheterisation may be required [488]. A study on female sexuality after cystectomy and orthotopic ileal neobladder showed pain relief in all patients and improvement in sexual function items in women who remained sexually active [489]. Pregnancies with subsequent lower-segment Caesarean section have been reported after ileocystoplasty [490].

4. Cystectomy and ileal conduit formation avoids the increased surgical complexity of a continent urinary diversion and is the favoured approach in patients with significantly impaired renal function. The technique is considered for patients with PBPS who develop recurrent pain in the augmented bladder, continent pouch after enterocystoplasty or continent urinary diversion. Re-tubularisation of a previously used bowel segment to form a urinary conduit has been recommended [491].

Complete removal of the bladder is more likely to lead to symptom improvement compared with leaving part (subtotal cystectomy) or the whole bladder *in situ* [480]. In keeping with this, reports that un-resected PBPS bladders cease to induce symptoms after loss of contact with urine are limited [100, 492].

Major surgery should be preceded by thorough pre-operative evaluation, with an emphasis on determining the relevant disease location and subtype. If major surgery is being considered the patient should be referred to a specialist centre experienced in managing CPPPS with a multi-disciplinary team approach.

Primary Prostate Pain Syndrome

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 PPPS. A large Chinese RCT of circumcision combined with a triple oral therapy (ciprofloxacin, ibuprofen, tamsulosin) vs. oral therapy alone has been published for patients with PPPS (total n=774) [493]. It is hypothesised that there may be some immunological interaction via pathogenic antigen presenting cells in the foreskin with CD4+ T cells causing auto-immunity to the prostate gland. They reported an improvement in total NIH-CPSI score and subdomain scores at twelve weeks. However, despite a large cohort, the study results are questionable because of the weak theoretical background, and a potential large placebo effect lacking a sham control. In addition, no long-term effectiveness has been reported. Before having an impact on recommendations, the results of this study have to be independently confirmed and the treatment effect must persist.

Primary Testicular Pain Syndrome

Microsurgical denervation of the spermatic cord can be offered to patients with testicular pain. In a long-term follow-up study, patients who had a positive result on blocking the spermatic cord were found to have a good result following denervation [494, 495].

Chronic Primary Anal and Abdominal Pain Syndrome

Chronic primary anal pain syndrome after stapled procedures, such as hemorrhoidopexy or stapled transanal rectal resection may respond to excision of the scarred staple line as shown in 21 consecutive patients with an overall improvement of pain in 85.7% of patients undergoing scar excision surgery [496]. An early scar excision before three to six months after pain onset was associated with better pain relief. Adhesiolysis is still in discussion in the pain management after laparotomy/laparoscopy for different surgical indications in the pelvis and entire abdomen. An RCT has shown, that adhesiolysis is associated with an increased risk of operative complications, and additional operations and increased health care costs as compared to laparoscopy alone [497].

Primary Urethral Pain Syndrome

There is no specific treatment that can be advised. Management should be multi-disciplinary and multi-modal [498]. 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 [499]. The majority of publications on treatment of primary urethral pain syndrome have come from psychologists [500, 501].

Presumed intra-abdominal adhesions

In gynaeocological patients with CPPPS and presumed adhesions, there is no consensus as to whether adhesiolysis should be performed to improve pain [501].

Extensive surgery for endometriosis is challenging and is still considered to be controversial, as there is at least one RCT showing no benefit in pain relief after the removal of early extensive endometriosis vs. sham surgery [262, 502]. Increasingly treatment algorithms are being developed using a multi-disciplinary approach, although none have thus far been proven clinically [503]. In patients with adenomyosis, the only curative surgery is hysterectomy but patients can benefit from hormonal therapy and analgesics (see Section 5.2.2).

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 [250, 504-508]. Currently, there has been only one prospective RCT (transgluteal approach) [507]. This study suggests that, if the patient has had the pain for less than six years, 66% of patients will see some improvement with surgery (vs. 40% if the pain has been present for more than six years). Surgery is not the answer for all patients. On talking to patients that have undergone surgery, providing the diagnosis was clear-cut, most patients were grateful to have undergone surgery but many still have symptoms that need management.

Chronic Pelvic Pain and Prolapse/Incontinence Mesh

Removing an existing mesh is a complex procedure [509]. Each patient is approached on an individual basis depending on the type of mesh and extent of complications [510]. The complexity of surgery often involves removal of dense scar tissue, reformation of inflamed vaginal skin and surgical reconstruction of the urethra and bladder [511]. Such surgery requires specialist skills, best provided within a multi-disciplinary tertiary setting. Possible complications as a result of this surgical removal include bleeding, infection, damage to surrounding organs as well as LUTS, persistent chronic pain and recurrent SUI, which occurs after mesh removal [512].

Removal of mesh, whilst complex, does have beneficial outcomes generally, which are also durable particularly for chronic pain [513]. However, the long-term consequences after the mesh is removed still can include, not only chronic persistent pain but also autoimmune responses and complex neuropathies affecting the pelvis and lower limbs [514, 515]. Some of these can be treated effectively using a multi-disciplinary pain medicine approach [516]. In other cases, the residual symptoms may require the input of an immunologist, rheumatologist or other symptom-defined specialist. The alternative to continence and prolapse mesh surgery is dependent on the clinical findings at the time. They include behavioural change, physiotherapy (for SUI and Grade I-II uterovaginal prolapse) or traditional surgical techniques. Studies have shown that over 70% who committed to physiotherapy for SUI often did not need any further intervention [517]. Many clinicians are reverting to conservative measures first, before re-considering surgery. Clinicians are also now retraining in traditional continence surgical techniques, which existed in the pre-mesh era, such as the Burch colposuspension and autologous fascial sling; as well as traditional utero-vaginal prolapse techniques such as vaginal hysterectomy, sacrospinous fixation and fascial repair of vaginal wall prolapse.

5.4 Summary of evidence and recommendations: management

*5.4.1 **Management of primary prostate pain syndrome***

Summary of evidence	**LE**
Phenotypically directed treatment may improve treatment success.	3
α-blockers have moderate treatment effect regarding total pain, voiding, and QoL scores in PPPS.	1a
Antimicrobial therapy has a moderate effect on total pain, voiding, and QoL scores in PPPS.	1a
Non-steroidal anti-inflammatory drugs have moderate overall treatment effects on PPPS.	1a
Phytotherapy has some beneficial effect on pain and overall favourable treatment response in PPPS.	1a
Pentosane polysulphate improves global assessment and QoL score in PPPS.	1b
There are insufficient data on the effectiveness of muscle relaxants in PPPS.	2b
Pregabalin is not effective for the treatment of PPPS.	1b

Botulinum toxin type A injection into the pelvic floor (or prostate) may have a modest effect in PPPS.	2b
Acupuncture is superior to sham acupuncture in improving symptoms and QoL.	1a
Posterior tibial nerve stimulation is probably effective for the treatment of PPPS.	1b
Extracorporeal shock wave therapy is probably effective over the short term.	1b
There are insufficient data supporting the use of other surgical treatments, such as transurethral incision of the bladder neck, transurethral resection of the prostate, or radical prostatectomy in patients with PPPS.	3
Cognitive behavioural therapy designed for PPPS may improve pain and QoL.	3

Recommendations	**Strength rating**
Offer multimodal and phenotypically directed treatment options for Primary Prostate Pain Syndrome (PPPS).	Weak
Use antimicrobial therapy (quinolones or tetracyclines) over a minimum of six weeks in treatment-naïve patients with a duration of PPPS less than one year.	Strong
Use α-blockers for patients with a duration of PPPS less than one year.	Strong
Offer high-dose oral pentosane polysulphate in PPPS.	Weak
Offer acupuncture in PPPS.	Strong
Offer non-steroidal anti-inflammatory drugs in PPPS, but long-term side-effects have to be considered.	Weak

5.4.2 Management of primary bladder pain syndrome

Summary of evidence	**LE**
There is insufficient data for the long-term use of corticosteroids.	3
Limited data exist on effectiveness of cimetidine in PBPS.	2b
Amitriptyline is effective for pain and related symptoms of PBPS.	1b
Oral pentosane polysulphate is effective for pain and related symptoms of PBPS.	1a
Oral pentosane polysulphate plus subcutaneous heparin is effective for pain and related symptoms of PBPS, especially in initially low responders to pentosane polysulphate alone.	1b
Intravesical lidocaine plus sodium bicarbonate is effective in the short term.	1b
Intravesical pentosane polysulphate is effective, based on limited data, and may enhance oral treatment.	1b
There are limited data on the effectiveness of intravesical heparin.	3
Intravesical chondroitin sulphate may be effective.	2b
There is insufficient data for the use of bladder distension as a therapeutic intervention.	3
Hydrodistension plus BTX-A is superior to hydrodistension alone.	1b
Intravesical BCG is not effective in PBPS.	1b
Transurethral resection (coagulation and laser) may be effective in PBPS type 3 C.	3
Sacral neuromodulation may be effective in PBPS.	3
Pudendal nerve stimulation is superior to sacral neuromodulation for treatment of PBPS.	1b
Avoidance of certain foods and drink may reduce symptoms.	3
Outcome of cystectomy for PBPS is variable.	3

Recommendations	**Strength rating**
Offer subtype and phenotype-oriented therapy for the treatment of Primary Bladder Pain Syndrome (PBPS).	Strong
Always consider offering multimodal behavioural, physical and psychological techniques alongside oral or invasive treatments of PBPS.	Strong
Offer dietary advice.	Weak
Administer amitriptyline for treatment of PBPS.	Strong

Offer oral pentosane polysulphate for the treatment of PBPS.	Strong
Offer oral pentosane polysulphate plus subcutaneous heparin in low responders to pentosane polysulphate alone.	Weak
Do not recommend oral corticosteroids for long-term treatment.	Strong
Offer intravesical hyaluronic acid or chondroitin sulphate before more invasive measures.	Weak
Offer intravesical lidocaine plus sodium bicarbonate prior to more invasive methods.	Weak
Offer intravesical heparin before more invasive measures alone or in combination treatment.	Weak
Do not use bladder distension alone as a treatment of PBPS.	Weak
Consider submucosal bladder wall and trigonal injection of botulinum toxin type A plus hydrodistension if intravesical instillation therapies have failed.	Strong
Offer neuromodulation before more invasive interventions.	Weak
Only undertake ablative and/or reconstructive surgery as the last resort and only by experienced and PBPS-knowledgeable surgeons, following a multi-disciplinary assessment including pain management.	Strong
Offer transurethral resection (or coagulation or laser) of bladder lesions, but in PBPS type 3 C only.	Strong

*5.4.3 **Management of scrotal pain syndrome***

Summary of evidence	**LE**
Microsurgical denervation of the spermatic cord is an effective therapy for primary scrotal pain syndrome.	2b
Vasovasostomy is effective in post-vasectomy pain.	2b

Recommendations	**Strength rating**
Inform about the risk of post-vasectomy pain when counselling patients planned for vasectomy.	Strong
Do open instead of laparoscopic inguinal hernia repair, to reduce the risk of scrotal pain.	Strong
In patients with testicular pain improving after spermatic block, offer microsurgical denervation of the spermatic cord.	Weak

*5.4.4 **Management of primary urethral pain syndrome***

Summary of evidence	**LE**
There is no specific treatment for primary urethral pain syndrome.	4

*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
Most gynaecological pain conditions (including dysmenorrhea, post-mesh insertion and gynaecological malignancy) can be treated effectively using pharmacotherapy.	3
All other gynaecological conditions (including obstetric injury, pelvic organ prolapse) can be treated effectively using surgery.	2

Recommendations	Strength rating
Involve a gynaecologist to provide therapeutic options such as hormonal therapy or surgery in well-defined disease states.	Strong
Provide a multi-disciplinary approach to pain management in persistent disease states.	Strong
All patients who have developed complications after mesh insertion should be referred to a multi-disciplinary service (incorporating pain medicine and surgery).	Strong

5.4.6 Management of primary anorectal pain syndrome

Summary of evidence	LE
Biofeedback is the preferred treatment for Chronic Primary Anal Pain Syndrome.	1a
Electro stimulation is less effective than biofeedback.	1b
Available evidence fails to confirm effectiveness of BTX-A in management of Chronic Primary Anal Pain Syndrome.	3
Percutaneous tibial nerve stimulation is effective in anal pain.	3
Sacral neuromodulation is effective in anal pain.	3
Inhaled salbutamol is effective in intermittent Chronic Primary Anal Pain Syndrome.	3

Recommendations	Strength rating
Undertake biofeedback treatment in patients with chronic anal pain.	Strong
Offer percutaneous tibial nerve stimulation in Chronic Primary Anal Pain Syndrome.	Weak
Offer sacral neuromodulation in Chronic Primary Anal Pain Syndrome.	Weak
Offer inhaled salbutamol in intermittent Chronic Primary Anal Pain Syndrome.	Weak

5.4.7 Management of pudendal neuralgia

Summary of evidence	LE
There are multiple treatment options with varying levels of evidence.	3

Recommendation	Strength rating
Neuropathic pain guidelines are well-established. Use standard approaches to management of neuropathic pain.	Strong

5.4.8 Management of sexological aspects in chronic pelvic pain

Summary of evidence	LE
Pelvic floor muscle physical therapy may offer relief of pain and reduction in sexual complaints.	2b

Recommendations	Strength rating
Offer behavioural strategies to the patient and his/her partner to reduce sexual dysfunctions.	Weak
Offer pelvic floor muscle therapy as part of the treatment plan to improve quality of life and sexual function.	Weak

5.4.9 Management of psychological aspects in chronic pelvic pain

Recommendation	Strength rating
For chronic pelvic pain with significant psychological distress, refer patient for chronic pelvic pain-focused psychological treatment.	Strong

*5.4.10 **Management of pelvic floor dysfunction***

Summary of evidence	LE
Myofascial treatment is effective.	1b
Biofeedback improves the outcome of myofascial therapy.	1a

Recommendations	Strength rating
Apply myofascial treatment as first-line treatment.	Weak
Offer biofeedback as therapy adjuvant to muscle exercises, in patients with anal pain due to an overactive pelvic floor.	Strong

*5.4.11 **Management of chronic/non-acute urogenital pain by opioids***

Recommendations	Strength rating
Opioids and other drugs of addiction/dependency should only be prescribed following multi-disciplinary assessment and only after other reasonable treatments have been tried and failed.	Strong
The decision to instigate long-term opioid therapy should be made by an appropriately trained specialist in consultation with the patient and their family doctor.	Strong
Where there is a history or suspicion of drug abuse, involve a psychiatrist or psychologist with an interest in pain management and drug addiction.	Strong

6. EVALUATION OF TREATMENT RESULTS

6.1 Evaluation of treatment

For patients with chronic primary visceral pain, a visit to the clinician is important because they can ask questions, talk about how the process is going and have some time with the caregiver who understands the nature of their pain. First evaluation should take place after about six weeks to see if the treatment has been successful or not. When necessary adaptations are made and a next evaluation is planned.

*6.1.1 **Treatment has not been effective***

6.1.1.1 Alternative treatment

In cases where the treatment initiated did not have enough effect, an alternative approach is advised. The first thing to do is a thorough evaluation of the patients' or care providers' adherence to the treatment that was initiated. Ask the patient if they have taken the medication according to the prescription, if there were any side effects and if there were any changes in pain and function. Adjustment of medication or dose schemes might help. Another important thing to do is to read the reports of other caregivers, for example, 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 terminated by the patient, ask the patient why they made that decision. Check if the patient has understood the idea behind the therapy that had been prematurely stopped.

6.1.1.2 Referral to next envelope of care

If patients and doctors conclude that none of the therapies given showed enough effect, then referral to a next envelope of care is advised. Unfortunately, the terminology used to describe the nature and specialisation level of centres providing specialised care for visceral pain patients is not standardised and is country-based. This does not facilitate easy referral schemes. It is advised that patients are referred to a centre that is working with a multi-disciplinary team and nationally recognised as specialised in pelvic pain. Such a centre will re-evaluate what has been done and when available, provide specialised care.

6.1.1.3 Self-management and shared care

Patients who find themselves confronted with CPPPS, for which there is no specific treatment option available, will have to live with their pain. They will need to manage their pain, meaning that they will have to find a way to deal with the impact of their pain on daily activities in all domains of life. Self-help programmes may be advised and can be of help. The patient may also benefit from shared care, which means that a caregiver is available for supporting the self-management strategies. Together with this caregiver, the patient can optimise and use the management strategies.

*6.1.2 **Treatment has been effective***

In cases where treatment has been effective, the caregiver may pay attention to fall-back prevention. If the patient feels the same pain again, it helps to start at an early stage with the self-management strategies that he/she has learned during the former treatment. By doing so they will have the best chance of preventing the re-development of pelvic pain syndromes.

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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 https://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.

9. CITATION INFORMATION

The format in which to cite the EAU Guidelines will vary depending on the style guide of the journal in which the citation appears. Accordingly, the number of authors or whether, for instance, to include the publisher, location, or an ISBN number may vary.

The compilation of the complete Guidelines should be referenced as:
EAU Guidelines. Edn. presented at the EAU Annual Congress Paris 2024. ISBN 978-94-92671-12-3.

If a publisher and/or location is required, include:
EAU Guidelines Office, Arnhem, The Netherlands. http://uroweb.org/guidelines/compilations-of-all-guidelines/

References to individual guidelines should be structured in the following way:
Contributors' names. Title of resource. Publication type. ISBN. Publisher and publisher location, year.

EAU Guidelines on

Neuro-Urology

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1. INTRODUCTION

1.1 Aim and objectives

The European Association of Urology (EAU) Neuro-Urology Guidelines aim to provide information for clinical practitioners on the incidence, definitions, diagnosis, therapy, and follow-up of neuro-urological disorders. These Guidelines reflect the current opinion of experts in this specific pathology and represent a state-of-the-art reference for all clinicians, as of the publication date.

The terminology used and the diagnostic procedures advised throughout these Guidelines follow the recommendations for investigations of the lower urinary tract (LUT) as published by the International Continence Society (ICS) [1-3]. Readers are advised to consult other EAU Guidelines that may address different aspects of the topics discussed in this document.

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

1.2 Panel composition

The EAU Neuro-Urology Guidelines Panel consists of an international multidisciplinary group of neuro-urological experts. All experts involved in the production of this document have submitted potential conflict of interest statements which can be viewed on the EAU website: http://www.uroweb.org/guideline/neuro-urology/.

1.3 Available publications

A quick reference document, the Pocket Guidelines, is available in print and as an app for iOS and Android devices. These are abridged versions which may require consultation with the full text version. A guideline summary has also been published in European Urology [4]. All are available through the EAU website: http://www.uroweb.org/guideline/neurourology/.

1.4 Publication history and summary of changes

*1.4.1 **Publication history***

The EAU Guidelines on Neuro-Urology were first published in 2003. Standard procedure for EAU Guidelines includes an annual assessment of newly published literature in the field to guide future updates. This 2024 Neuro-Urology Guidelines present an update of the 2022 publication.

*1.4.2 **Summary of changes***

All chapters of the 2024 Neuro-Urology Guidelines have been updated, based on the 2023 version of the Guidelines. References have been added throughout the document resulting in various text updates and changes in evidence summaries and recommendations including but not limited to:

- Updates throughout Table 1 and the inclusion of data for Myasthenia gravis.
- A new recommendation for blood pressure and heartrate monitoring in section 3.3.7.4
- A new paragraph on other drugs used as medical therapy for neuro-urological symptoms in section 3.4.2.3 as well as a new summary of evidence (SOE) and recommendation for mirabegron in section 3.4.2.4
- Multiple text updates in section 3.4.3. on the various surgical intervention options for SUI in neuro-urological patients.
- A new SOE and recommendation for sacral neuromodulation in section 3.4.3.6
- A new recommendation against the use of dipstick urine analysis to screen for UTI in neuro-urological patients in section 3.5.4.

1.5 Background

The function of the LUT is mainly storage and voiding of urine, which is regulated by the nervous system that co-ordinates the activity of the urinary bladder and bladder outlet. The part of the nervous system that regulates LUT function is disseminated from the peripheral nerves in the pelvis to highly specialised cortical areas. Any disturbance of the nervous system involved, can result in neuro-urological symptoms. The extent and location of the disturbance will determine the type of LUT dysfunction, which can be symptomatic or asymptomatic. Neuro-urological symptoms can cause a variety of long-term complications; the most significant being deterioration of renal function. Since symptoms and long-term complications do not correlate [5], it is important to identify patients with neuro-urological symptoms, and establish if they have a low or high risk of subsequent

complications. The risk of developing upper urinary tract (UUT) damage and renal failure is much lower in patients with slowly progressive non-traumatic neurological disorders than in those with spinal cord injury or spina bifida [6]. In summary, treatment and intensity of follow-up examinations are based on the type of neuro-urological disorder and the underlying cause.

2. METHODS

2.1 Introduction

For the 2024 Neuro-Urology Guidelines, new and relevant evidence has been identified, collated, and appraised through a structured assessment of the literature. A broad and comprehensive literature search, covering all sections of the Neuro-Urology Guidelines was performed. Databases searched included Medline, EMBASE, and the Cochrane Libraries, covering a time frame between the 1st of May 2021 and 1st May 2023. A total of 1,896 unique records were identified, retrieved, and screened for relevance. A detailed search strategy is available online: http://uroweb.org/guideline/neuro-urology/?type=appendices-publications.

Recommendation within the Guidelines are developed by the panels to prioritise clinically important care decisions. The strength of each recommendation is determined by the balance between desirable and undesirable consequences of alternative management strategies, the quality of the evidence (including certainty of estimates), and the nature and variability of patient values and preferences. This decision process, which can be reviewed in the strength rating forms which accompany each guideline statement, addresses a number of key elements:

1. the overall quality of the evidence which exists for the recommendation [7];
2. the magnitude of the effect (individual or combined effects);
3. the certainty of the results (precision, consistency, heterogeneity and other statistical or study related factors);
4. the balance between desirable and undesirable outcomes;
5. the impact and certainty of patient values and preferences on the intervention.

Strong recommendations typically indicate a high degree of evidence quality and / or a favourable balance of benefit to harm and patient preference. Weak recommendations typically indicate availability of lower quality evidence, and/or equivocal balance between benefit and harm, and uncertainty or variability of patient preference [8].

Additional methodology information and a list of associations endorsing the EAU Guidelines can be found in the online: https://uroweb.org/eau-guidelines/methodology-policies.

2.2 Review

Publications ensuing from panel-lead systematic reviews (SR) have all been peer-reviewed. The 2024 Neuro-Urology Guidelines were subject to peer review prior to publication.

3. THE GUIDELINE

3.1 Epidemiology, aetiology and pathophysiology

3.1.1 Introduction

Neuro-urological symptoms may be caused by a variety of diseases and events affecting the nervous system controlling the LUT. The resulting neuro-urological symptoms depend predominantly on the location and the extent of the neurological lesion. There are no exact figures on the overall prevalence of neuro-urological disorders in the general population, but data are available on the prevalence of the underlying conditions and the relative risk of these for the development of neuro-urological symptoms. It is important to note that the majority of the data shows a very wide range of prevalence/incidence. This reflects the variability in the cohort (e.g., early or late-stage disease) and the frequently small sample sizes, resulting in a low level of evidence in most published data (summarised in Table 1).

Table 1: Epidemiology of Neuro-Urological Disorders

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) [9], 10% of cardiovascular mortality.	Nocturia - overactive bladder (OAB) - urgency urinary incontinence (UUI) – neurogenic detrusor overactivity (NDO), other patterns less frequent [10]. 57-83% of neuro-urological symptoms at one month post-stroke, 71-80% spontaneous recovery at six months [11]. Persistence of urinary incontinence (UI) correlates with poor prognosis [12].
Dementias: Alzheimer's disease (80%), Vascular (10%), Other (10%).	6.4% of adults > 65 yrs [13].	OAB - UUI – NDO, 25% of incontinence in Alzheimer's disease, > 25% in other dementias: Lewy body, NPH, Binswanger, Nasu-Hakola, Pick Disease [14]. Incontinence three times more frequent in geriatric patients with dementia than without [15].
Parkinsonian syndrome (PS) Idiopathic Parkinson's disease (IPD): 75-80% of PS.	Second most prevalent neurodegenerative disease after Alzheimer's disease. Rising prevalence of IPD with age [16].	LUTS affect 50% at onset, with urgency and nocturia being the most common. Patients with LUTS at presentation have worse disease progression in Parkinson's disease [17]. LUTS prevalence data depend on gender, age, and Hoehn and Yahr stage [18].
Non-IPD: Parkinson's-plus (18%): - Multiple system atrophy (MSA), - Progressive supranuclear palsy, - Corticobasal degeneration, - Dementia with Lewy bodies. Secondary Parkinson's (2%)	MSA is the most frequent non-IPD PS.	Infections account for a major cause of mortality in MSA [19]. Impaired detrusor contractility with post-void residual (PVR) > 150 mL seems to be the urodynamic finding distinguishing MSA from IPD [20-22].
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].	32-46% of patients with cerebral palsy suffer from UI, with 85% of patients having abnormal urodynamic studies (NDO most common 59%). Upper tract deterioration is rare (2.5%) [26, 27].
Traumatic brain injury	235/100,000/yr [28].	44% storage dysfunction, 38% voiding dysfunction, 60% urodynamic abnormalities [29].
Normal pressure hydrocephalus	0.5% of the population > 60, up to 2.9% of those > 65 [30].	Classic triad of gait and cognitive disturbance along with neurogenic lower urinary tract dysfunction (NLUTD). The latter is mainly related to NDO and affects 76-83% of patients [30].

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 [31].	NDO and detrusor sphincter dyssynergia (DSD) (up to 95%) and detrusor underactivity (DU) (up to 83%) depending on the level of the lesion [32].
Spina bifida (SB)	Spina bifida 3-4/10,000 Lumbar and lumbosacral form are the most common (60%) [33].	Bladder function is impaired in up to 96% of SB patients [34]. Over 50% of patients are incontinent [35]. Patients with open and closed defects can have equally severe NLUTD [36].
Hereditary spastic paraplegia (HSP)	Prevalence 1.3-9/100,000 [37].	LUTS in about 75%, mainly urgency and voiding dysfunction NDO in 81% (of whom 76% with DSD) [37]
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 lumbosciatic episode related to disc prolapse. Incidence: approx. 5/100,000/yr More common in females > 45 yr.	26% difficulty to void and acontractile detrusor [38]. Detrusor underactivity (up to 83%) [32]. Tarlov cysts: early sensation of filling (70%), NDO (33%), and stress urinary incontinence (SUI) (33%) [39].
Iatrogenic pelvic nerve lesions	Rectal cancer. Cervical cancer (multimodal therapy, radiotherapy and surgery). Endometriosis surgery.	After abdomino-perineal resection: 50% urinary retention. After total mesorectal excision: 10-30% voiding dysfunction [40].
Peripheral neuropathy Diabetes Other causes of peripheral neuropathy causing neuro-urological symptoms: - Alcohol abuse; - Lumbosacral zone and genital herpes; - Guillain Barre syndrome; - Porphyria; - and Sarcoidosis.	Worldwide, prevalence of pharmacologically treated diabetes 8.3% [41].	OAB +/- UUI [42]. Hypersensitivity and DU at later phase [42].
Myasthenia gravis	Prevalence 20/100,000 [43]	Increased daytime frequency, nocturia, incontinence [43]
Disseminated central diseases		
Multiple sclerosis (MS)	Prevalence: 83/100,000 in Europe [44].	10% of MS patients present with voiding dysfunction at disease onset, 75% of patients will develop it after 10 yrs of MS [45]. NDO: 65% [45], 43% [46]. DSD: 35% [45, 46]. DU: 25% [45].

3.2 Classification systems

3.2.1 Introduction

Relevant definitions can be found in the general ICS standardisation reports [2, 3, 47, 48]. Supplementary online Tables S1 and S2 list the definitions from these references, partly adapted, and other definitions considered useful for clinical practice: https://uroweb.org/guideline/neuro-urology/?type=appendices-publications. A classification system that also includes UUT dysfunction in neuro-urological patients has also been described [48].

3.3 Diagnostic evaluation

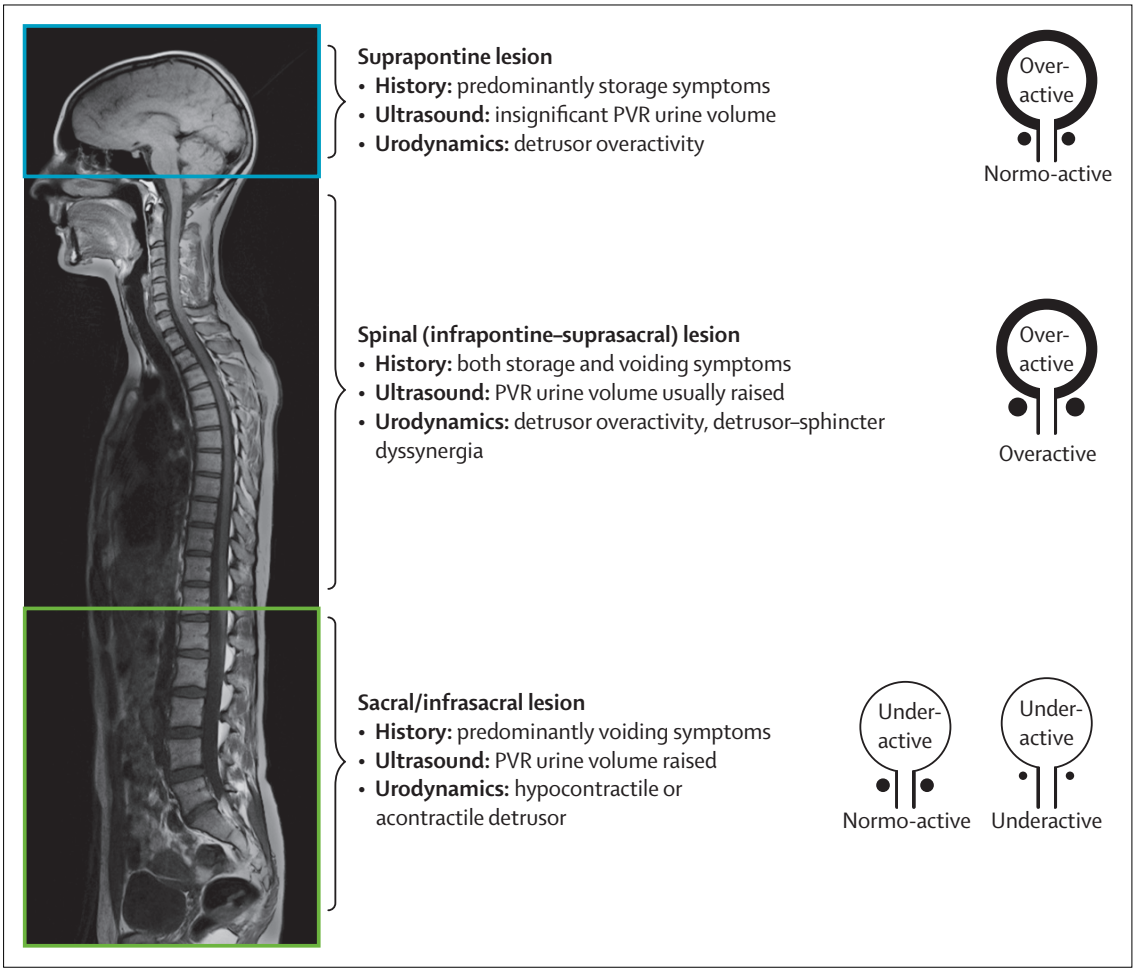
3.3.1 Introduction

The normal physiological function of the LUT depends on an intricate interplay between the sensory and motor nervous systems. When diagnosing neuro-urological symptoms, the aim is to describe the type of dysfunction involved. A thorough medical history, physical examination and bladder diary are mandatory before any additional diagnostic investigations can be planned. Results of the initial evaluation are used to decide the patient's long-term treatment and follow-up.

3.3.2 Classification systems

The pattern of LUT dysfunction following neurological disease is determined by the site and nature of the lesion. A very simple classification system for use in daily clinical practice to decide on the appropriate therapeutic approach is provided in Figure 1 [6].

Figure 1: Patterns of lower urinary tract dysfunction following neurological disease



The pattern of LUT dysfunction following neurological disease is determined by the site and nature of the lesion. Panel (A) denotes the region above the pons, panel (B) the region between the pons and the sacral cord and panel (C) the sacral cord and infrasacral region. Figures on the right show the expected dysfunctional states of the detrusor-sphincter system. Figure adapted from Panicker et al., [6] with permission from Elsevier.
PVR = post-void residual.

3.3.3 Timing of diagnosis and treatment

Early diagnosis and treatment are essential in both congenital and acquired neuro-urological disorders. This helps to prevent irreversible changes within the LUT, even in the presence of normal reflexes [49]. Furthermore, urological symptoms can be the presenting feature of neurological pathology [50, 51]. Early intervention can prevent irreversible deterioration of the LUT and UUT [51]. Long term follow-up (life-long) is mandatory to assess risk of UUT damage and renal failure [52, 53].

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 selection of 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 [54].
- Urinary history consists of symptoms associated with both urine storage and voiding.
- Bowel history is important because patients with neuro-urological symptoms may also have related neurogenic bowel dysfunction [55].
- Sexual function may be impaired because of the neuro-urological condition [56].
- 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 urinary tract infection (UTI)-related symptoms accurately [57, 58].
- The presence of urinary, bowel and sexual symptoms without neurological symptoms could be suggestive of an underlying neurological disease or condition.
- The severity of lesion after acute SCI does not predict the presence or absence of unfavourable urodynamic parameters [49].

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 (painful, abnormal, absent or increased)
Initiation of micturition (normal, precipitate, reflex, strain, Credé)
Interruption of micturition (normal, paradoxical, passive)
Enuresis
Mode and type of voiding (catheterisation)
Frequency, voided volume, stress/urgency/mixed urinary incontinence, urgency episodes

Sexual history
Genital or sexual dysfunction symptoms
Sensation in genital area (absent, increased, abnormal, pain)
Specific male: libido, erection, (lack of) orgasm, ejaculation
Specific female: libido, dyspareunia, (lack of) orgasm
Bowel history
Type of bowel program
Frequency and faecal incontinence
Desire to defecate
Defecation pattern
Rectal sensation
Initiation of defecation (digital stimulation, enema, suppositories)
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 (AD) (especially in lesions at or above level Th 6)
Mobility and hand function

3.3.4.1 Bladder diaries

Bladder diaries are considered a valuable diagnostic tool for the initial assessment of neurogenic LUT dysfunction. They provide data on the number of voids (spontaneous or intermittent catheter), voided volume, stress/urgency/mixed urinary incontinence episodes and contribute to the interpretation of urodynamic testing. Preferably, bladder diaries should be completed for three consecutive days [59].

3.3.5 ***Patient quality of life questionnaires***

Quality of life (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 [60]. The type of bladder management has been shown to affect health-related QoL (HRQoL) mainly in patients with SCI [61, 62] and MS [63], as does the presence or absence of urinary, sexual and faecal incontinence [64]. 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 [65].

In recent years a proliferation in the number of questionnaires to evaluate symptoms and QoL has been seen. Condition-specific questionnaires can be used to assess symptom severity and the impact of symptoms on QoL. A patient's overall QoL can be assessed using generic questionnaires. It is important that the questionnaire of choice has been validated in the neuro-urological population, and that it is available in the language that it is to be used in.

3.3.5.1 Available Questionnaires

Three condition-specific questionnaires for urinary or bowel dysfunction and QoL have been developed specifically for adult neuro-urological patients [63]. In MS and SCI patients the Qualiveen, also available in a short version, is validated and translated into various languages [66, 67]. Although several objective and subjective tools have been used to assess the influence of neurogenic lower urinary tract dysfunctions (N-LUTD) on QoL in SCI, the Quality life index-SCI and Qualiveen are the only validated condition-specific outcomes that have shown consistent sensitivity [68]. The Neurogenic Bladder Symptom Score (NBSS) and its short version has been validated in neurological patients to measure urinary symptoms and their consequences [69-71]. The QoL scoring tool related to Bowel Management (QoL-BM) [72] can be used to assess bowel dysfunction in MS and SCI patients. A new tool has recently been developed to understand the reasons for poor compliance in long-term management of neurogenic patients. [73, 74]. A variety of patient-reported outcome measures (PROMs) are available to evaluate sexual function in neuro-urological patients. However, only the Multiple Sclerosis Intimacy and Sexuality Questionnaire-15 (MSISQ-15) and -19 is supported by evidence [75-77].

In addition, several validated questionnaires that evaluate QoL and assess urinary symptoms as a subscale or question in neuro-urological patients have been identified [78] (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 [79].

A patient's overall QoL can be assessed by generic HRQoL questionnaires, the most commonly used being the I-QOL, King's Health Questionnaire (KHQ), or the Short Form 36-item and 12-item Health Survey Questionnaires (SF-36, SF-12) [80]. In addition, the quality-adjusted life year (QALY), quantifies outcomes, by weighing years of life spent in a specified health state, adjusted by a factor representing the value placed by society or patients on their specific health state [81].

No evidence was found for which validated questionnaires are the most appropriate for use, since no quality criteria for validated questionnaires have been assessed [80].

Table 5: Patient questionnaires

Questionnaire	Underlying neurological disorder	Bladder	Bowel	Sexual function
FAMS [82]	MS	X		X
FILMS [83]	MS	X	X	
HAQUAMS [84]	MS	X	X	X
I-QOL [79]	MS, SCI	X		X
LUTS-TCA [73]	MS, SCI, Parkinson	X		
MDS [85]	MS	X	X	
MSISQ-15 / MSISQ-19 [75, 76]	MS, SCI	X	X	X
MSQLI [86]	MS	X	X	X
MSQoL-54 [87]	MS	X	X	X
MSWDQ [88]	MS	X	X	
NBSS [69, 71]	MS, SCI, SB, Cerebral Palsy	X		
NBSS-SF [70]	MS, SCI, SB	X		
QoL-BM [72]	SCI		X	
Qualiveen/SF-Qualiveen [67, 89]	MS, SCI	X		X
RAYS [90]	MS	X		X
RHSCIR [91]	SCI	X	X	X
USQNB [74]	SCI	X	X	

*3.3.6 **Physical examination and additional tests***

In addition to a detailed patient history, attention should be paid to possible physical and intellectual disabilities with respect to the planned investigations [92, 93]. Neuro-urological status should be described as completely as possible (Figure 2) [6]. Patients with a high spinal cord lesion or supraspinal neurological lesions may suffer from a significant drop in blood pressure when moved into a sitting or standing position. All sensations and reflexes in the urogenital area must be tested [6]. Furthermore, detailed testing of the anal sphincter and pelvic floor functions must be performed (Figure 2) [6, 94]. It is essential to have this clinical information to reliably interpret later diagnostic investigations (Table 6).

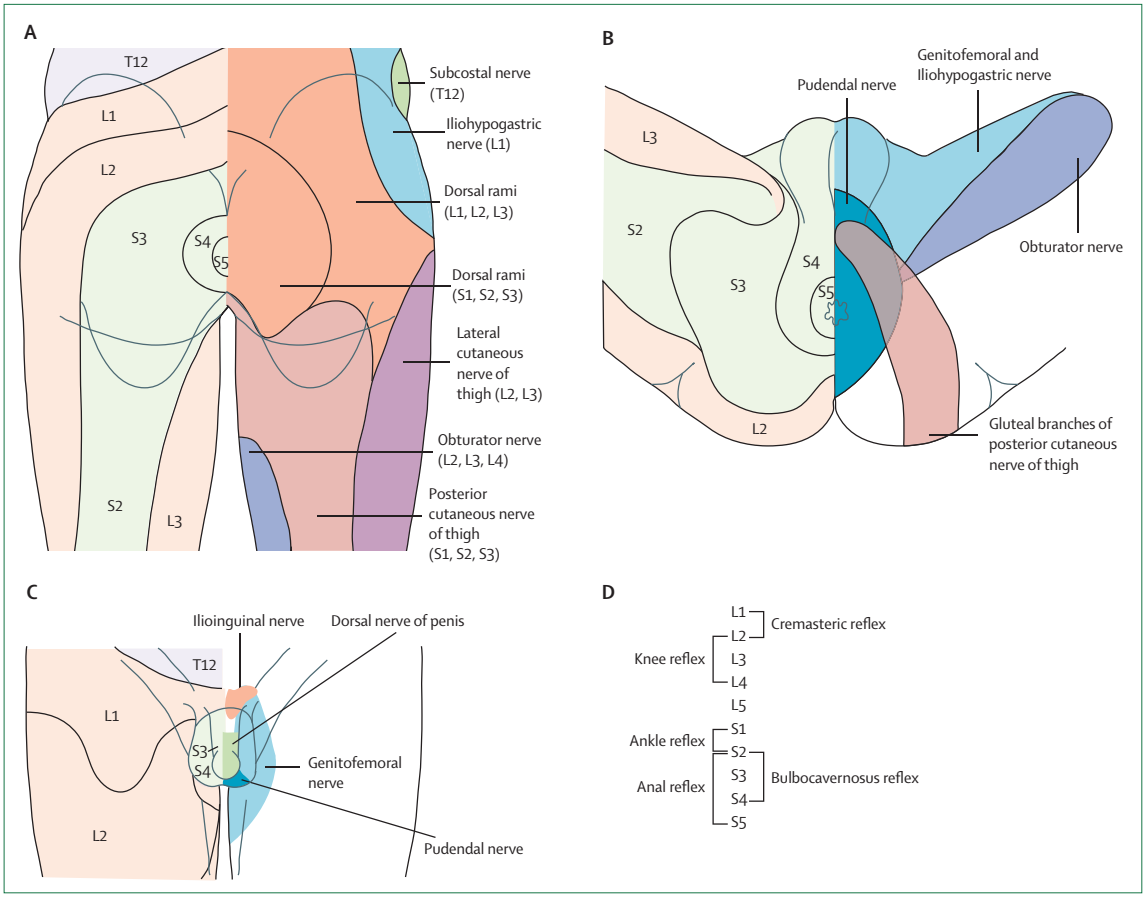
Additionally, urinalysis, blood chemistry, ultrasonography, post-void residual when indicated, incontinence quantification and were indicated free uroflowmetry, should be performed as part of the routine assessment of neuro-urological patients [6, 95].

3.3.6.1 Autonomic dysreflexia

Autonomic dysreflexia (AD) is a sudden and exaggerated autonomic response to various stimuli generally manifests in patients with SCI or spinal dysfunction at or above level Th 6. It is defined by an increase in systolic blood pressure > 20 mmHg from baseline and it is usually accompanied by a severe headache, blurred vision, feeling of anxiety, heart rate changes, as well as above the lesion, perspiration, piloerection, warm skin and flushing and below the lesion, pallor, cold skin, and sweating in the lower part of the body [96, 97]. Autonomic dysreflexia can have life-threatening consequences if not managed adequately. The stimulus can be distended

bladder or bowel (e.g., iatrogenic stimuli during cystoscopy or urodynamics) [98], but it can also be secondary to any noxious stimulus (e.g., infected toenail or pressure sore) or after sexual stimulation.

Figure 2: Lumbosacral dermatomes, cutaneous nerves, and reflexes



The physical examination includes testing sensations and reflexes mediated through the lower spinal cord. Abnormal findings would suggest a lesion affecting the lumbosacral segments; mapping out distinct areas of sensory impairment helps to further localise the site of the lesion. Distribution of dermatomes (areas of skin mainly supplied by a single spinal nerve) and cutaneous nerves over the perianal region and back of the upper thigh (A), the perineum [99] (B), male external genitalia [100] (C) and root values of lower spinal cord reflexes (D). Figure adapted from Panicker et al., [6] with parts A-C adapted from Standring [101], both with permission from Elsevier.

Table 6: Neuro-urological 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)

General urogenital assessment
Prostate palpation
Skin lesions
Size and presence of penis
Descensus (prolapse) of pelvic organs

3.3.6.2 Summary of evidence and recommendations for history taking and physical examination

Summary of evidence	LE
Early diagnosis and treatment are essential in both congenital and acquired neuro-urological disorders to prevent irreversible changes within the LUT.	4
An extensive general history is the basis of evaluation focusing on past and present symptoms including urinary, sexual, bowel and neurological function.	4
Assessment of present and expected future QoL is an essential aspect of the overall management of neuro-urological patients and is important to evaluate the effect of any therapy.	2a
Quality of life assessment should be completed with validated QoL questionnaires for neuro-urological patients.	1a
Bladder diaries provide data on the number of voids, voided volume, urinary incontinence, and urgency episodes.	3

Recommendations	Strength rating
Take an extensive general history, concentrating on past and present symptoms.	Strong
Take a specific history for each of the four mentioned functions - urinary, bowel, sexual and neurological.	Strong
Pay special attention to the possible existence of alarm symptoms/signs (e.g. pain, infection, haematuria, fever) that warrant further specific diagnosis.	Strong
Assess quality of life when evaluating and treating neuro-urological patients.	Strong
Use available validated tools for urinary and bowel symptoms in neuro-urological patients.	Strong
Use MSISQ-15 or MSISQ-19 to evaluate sexual function in multiple sclerosis patients.	Strong
Acknowledge individual patient disabilities when planning further investigations.	Strong
Describe the neurological status as completely as possible, sensations and reflexes in the urogenital area must all be tested.	Strong
Test the anal sphincter and pelvic floor functions.	Strong
Perform urinalysis, blood chemistry, bladder diary, post-void residual, incontinence quantification and urinary tract imaging as initial and routinary evaluation.	Strong

MSISQ 15/19 = Multiple Sclerosis Intimacy and Sexuality Questionnaire 15/19 question version.

*3.3.7 **Urodynamics***

3.3.7.1 Introduction

Urodynamic investigation is the only method that can objectively assess the function and dysfunction of the LUT. In neuro-urological patients, invasive urodynamic investigation is even more challenging than in general patients. Any technical source of artefacts must be critically considered. It is essential to maintain the quality of the urodynamic recording and its interpretation [1]. Same session repeat urodynamic investigations are crucial in clinical decision making, since repeat measurements may yield completely different results [102].

In patients at risk of AD, blood pressure (BP) and heartrate monitoring during the urodynamic study and other invasive procedures is mandatory [97, 103]. The rectal ampulla should be empty of stool before the start of the investigation. All urodynamic findings must be reported in detail and performed, according to the ICS technical recommendations and standards [1, 104].

In patients with SCI, first urodynamic investigation should take place within 3 months after SCI to facilitate early diagnosis of unfavourable urodynamic parameters and timely treatment [105] but there is need for further research regarding the urodynamic follow-up schedule during the first year after SCI [106].

3.3.7.2 Urodynamic tests

Free uroflowmetry and assessment of residual urine: It is recommended prior to planning any invasive urodynamics that patients are able to void in the usual position. For reliable information, it should be repeated at least two to three times [1]. Possible pathological findings include a low flow rate, low voided volume, intermittent flow, hesitancy and PVR.

Filling cystometry: This test is the only method for quantifying the patient's filling function. The status of LUT function must be documented during the filling phase. However, this technique has limited use as a solitary procedure. It is much more effective combined with bladder pressure measurement during micturition and is even more effective in video-urodynamics.

The bladder should be empty at the start of filling. A physiological filling rate should be used with body-warm saline. Possible pathological findings include neurogenic detrusor overactivity (NDO), low bladder compliance, abnormal bladder sensations, low cystometric capacity and urinary incontinence.

Detrusor leak point pressure [107]: Appears to have no use as a diagnostic tool. Some positive findings have been reported [52, 108, 109], but sensitivity is too low to estimate the risk to the UUT or for secondary bladder damage [110, 111].

Pressure flow study (or voiding cystometry): Reflects the coordination between detrusor and urethra or pelvic floor during the voiding phase. It is even more effective if combined with filling cystometry and video-urodynamics. Possible pathological findings include detrusor underactivity, acontractility, bladder outlet obstruction (BOO), DSD, a high urethral resistance, and residual urine.

Most types of obstruction caused by neuro-urological disorders are due to DSD [112, 113], non-relaxing urethra, and/or non-relaxing bladder neck [114, 115]. Pressure-flow analysis mainly assesses the amount of mechanical obstruction caused by the urethra's inherent mechanical and anatomical properties.

Electromyography (EMG): Reflects the activity of the external urethral sphincter, the peri-urethral striated musculature, the anal sphincter, and the striated pelvic floor muscles. Correct interpretation may be difficult due to artefacts introduced by other equipment. In the urodynamic setting, an EMG is useful as a gross indication of the patient's ability to control the pelvic floor. Possible pathological findings include inadequate recruitment upon specific stimuli (e.g. bladder filling, involuntary detrusor contractions, onset of voiding, coughing, Valsalva manoeuvre) suggesting a diagnosis of DSD [116].

Urethral pressure measurement: Has a very limited role in neuro-urological disorders. There is no consensus on parameters indicating pathological findings [117].

Video-urodynamics: Is the combination of filling cystometry and pressure flow studies with imaging. It is the optimum procedure for urodynamic investigation in neuro-urological disorders [5]. Possible pathological findings include all those described in the filling cystometry and the pressure flow study sections, and any morphological pathology of the LUT and reflux to the UUT [118].

Ambulatory urodynamics: This is the functional investigation of the urinary tract, which predominantly uses the natural filling of the urinary tract to reproduce the patient's normal activity. Although this type of study might be considered when conventional urodynamics does not reproduce the patient's symptoms, its role in the neuro-urological patient still needs to be determined [119, 120].

Triggered tests during urodynamics: Lower urinary tract function can be provoked by coughing, triggered voiding, or anal stretch. Fast-filling cystometry with cooled saline (the 'ice water test') was initially described to discriminate between upper and lower motor neuron lesions [121, 122]. Patients with upper motor neuron lesions develop a detrusor contraction if the detrusor is intact, while patients with lower motor neuron lesions do not. However, the test does not seem to be fully discriminative since also non neurological and lower motor SCI have shown positive test [123, 124].

Previously, a positive bethanechol test [125] (detrusor contraction > 25 cm H2O) was thought to indicate detrusor denervation hypersensitivity and the muscular integrity of an acontractile detrusor. However, in practice, the test has given equivocal results. A variation of this method was reported using intravesical electromotive administration of the bethanechol [126], 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 [127]:

- 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 Summary of evidence and recommendations for urodynamics and uro-neurophysiological tests

Summary of evidence	**LE**
Urodynamic investigation is the only method that can objectively assess the (dys-)function of the LUT.	2a
Video-urodynamics is the optimum procedure for urodynamic investigation in neuro-urological disorders.	4
Specific uro-neurophysiological tests are elective procedures and should only be carried out in specialised settings.	4

Recommendations	**Strength rating**
Perform a urodynamic investigation to detect and specify lower urinary tract (dys-)function, use same session repeat measurement as it is crucial in clinical decision making.	Strong
Non-invasive testing is mandatory before invasive urodynamics is planned.	Strong
Use video-urodynamics for invasive urodynamics in neuro-urological patients. If this is not available, then perform a filling cystometry continuing into a pressure flow study.	Strong
Use a physiological filling rate and body-warm saline.	Strong
Perform blood pressure and heartrate monitoring during urodynamic investigation and other invasive procedures in patients at risk for autonomic dysreflexia.	Strong

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 [128, 129]. Patients with SCI or SB have a higher risk of developing renal failure compared with patients with slowly progressive non-traumatic neurological disorders, such as MS and Parkinson's disease (PD) [130].

Caregivers must be informed of this risk and instructed to watch carefully for any signs or symptoms of a possible deterioration in the patient's renal function. In patients with poor muscle mass cystatin C based glomerular filtration rate (GFR) seems to be more accurate in detecting chronic kidney disease than serum creatinine estimated GFR [131]. There are no high-level evidence publications available which show the optimal management to preserve renal function in these patients [132].

3.4 Disease management

3.4.1 ***Introduction***

The primary aims for treatment of neuro-urological symptoms, and their priorities, are [129, 130]:

- protection of the UUT;
- achievement (or maintenance) of urinary continence;
- restoration of LUT function;
- improvement of the patient's QoL.

Further considerations are the patient's disability, cognition, social support, caregiver support, cost-effectiveness, technical complexity and possible complications [134].

Historically, renal failure was the main mortality factor in SCI patients who survived the trauma [135, 136]. Keeping the detrusor pressure during both the filling and voiding phases within safe limits significantly reduces the mortality from urological causes in these patients [137-139] and has consequently become the top priority in the treatment of patients with neuro-urological symptoms [133, 134].

In patients with high detrusor pressure during the filling phase (NDO, 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 [133]. Reduction of the detrusor pressure contributes to urinary continence, and consequently to social rehabilitation and QoL. It is also critical for preventing UTIs [140, 141]. However, complete continence cannot always be obtained.

*3.4.2 **Non-invasive conservative treatment***

3.4.2.1 Assisted bladder emptying - Credé manoeuvre, Valsalva manoeuvre, triggered reflex voiding

Incomplete bladder emptying is a serious risk factor for UTI, high intravesical pressure and incontinence. Methods to improve the voiding process should therefore be practiced.

Bladder expression: 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 [142, 143]. 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 [144, 145]. Therefore, their use should be discouraged unless urodynamics show that the intravesical pressure remains within safe limits [134].

Long-term complications are unavoidable for both methods of bladder emptying [143]. The already weak pelvic floor function may be further impaired, thus introducing or exacerbating already existing SUI [145].

Triggered reflex voiding: Stimulation of the sacral or lumbar dermatomes in patients with a upper motor neuron lesion can elicit a reflex detrusor contraction [145]. The risk of high pressure voiding is present and interventions to decrease outlet resistance may be necessary [146]. Triggering can induce AD, especially in patients with high level SCI (at or above Th 6) [147]. 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 [145, 148, 149].

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. Condom catheters with urine collection devices are a practical method for men [134]. The penile clamp is absolutely contraindicated in case of NDO or low bladder compliance due to 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 [134, 150]. The first mechanism is affected by activation of efferent nerve fibres, and the latter ones are produced by activation of afferent fibres [110]. Electrical stimulation of the pudendal nerve afferents, strongly inhibits the micturition reflex and detrusor contraction [151]. This stimulation might then support the restoration of the balance between excitatory and inhibitory inputs at the spinal or supraspinal level [134, 152]. Evidence for bladder rehabilitation using electrical stimulation in neurological patients is mainly based on small non-comparative studies with a high risk of bias.

Behavioural therapy and bladder training: In patients with PD, behavioural therapy and bladder training may be considered based on randomised controlled trials (RCTs) with very limited number of patients [153, 154].

Pelvic floor muscle training (PFMT): In patients with MS and stroke, PFMT may have positive effects on LUTS, daytime urinary frequency and urinary incontinence but the evidence is still limited [155, 156].

Peripheral temporary electrostimulation: Tibial nerve stimulation and transcutaneous electrical nerve stimulation (TENS) might be effective and safe for treating neurogenic LUT dysfunction, but more reliable evidence from well-designed RCTs is required to reach definitive conclusions [152, 157, 158]. In post-stroke patients TENS has been shown to effectively improve urodynamic and bladder diary findings as well as QoL [159-161]. In an RCT, transcutaneous tibial nerve home stimulation has proven to significantly improve bladder diary parameters in patients with MS as well as in women with PD [162, 163]. In acute SCI, TENS is able to achieve bladder neuromodulation via modulation of the autonomous nervous system functions [164]. Greater volumes until full sensation, less detrusor-sphincter dyssynergia and an increased bladder capacity can be found when compared to sham-treated patients [165].

A SR on dorsal genital nerve stimulation showed higher relative and absolute bladder capacities and inhibition of detrusor hyperactivity in SCI people, although these therapeutic effects may be dependent on the current, amplitude and longer periods of stimulation [166].

Interferential medium frequency current electrical stimulation for SCI patients with American spinal cord injury association impairment scale (AIS) levels B, C and D demonstrated a significant decrease in PVR and volume of urine leakage between catheterisation [167]. Neuromuscular electrical stimulation applied in the sacral area has also improved the performance in symptoms scores in highly selected patients with UI after stroke [160]; however, new RCTs with more patients and longer follow-up are required.

Peripheral temporary electrostimulation combined with pelvic floor muscle training and biofeedback: In MS patients, combining active neuromuscular electrical stimulation with Pelvic Floor Muscle Training (PFMT) and EMG biofeedback can achieve a substantial reduction of neuro-urological symptoms [168, 169]. This treatment combination seems to be more effective than either therapy alone [170, 171]. However, the combination of intravaginal electrostimulation and PFMT was not superior to PFMT alone in reducing UI in women with incomplete SCI [172].

Intravesical electrostimulation: Intravesical electrostimulation can increase bladder capacity and improve bladder filling sensation in patients with incomplete SCI or myelomeningocele (MMC) [173]. In patients with neurogenic detrusor underactivity, intravesical electrostimulation may also improve voiding and reduce residual volume [174, 175].

Repetitive transcranial magnetic stimulation: Although improvement of neuro-urological symptoms has been described in PD, SCI and MS patients, this technique is still under investigation [176]. The role of cortical as well as sacral magnetic stimulation in MS patients with underactive bladder needs to be better defined [177].

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 always available. Commonly, a combination of different therapies (e.g. intermittent catheterisation and antimuscarinic drugs) is advised to prevent urinary tract damage and improve long-term outcomes, particularly in patients with a suprasacral SCI or MS [145, 178-180]. Drug treatments are categorised depending on their mechanism of action and focus on storage or voiding symptoms.

3.4.2.3.1 Drugs for storage symptoms

Antimuscarinic drugs: are the first-line choice for treating NDO, increasing bladder capacity and reducing episodes of UI secondary to NDO by the inhibition of parasympathetic pathways [134, 181-187]. Antimuscarinic drugs have been used for many years to treat patients with NDO [185, 186, 188], and the responses of individual patients to antimuscarinic treatment are variable. Despite a meta-analysis confirming the clinical and urodynamic efficacy of antimuscarinic therapy compared to placebo in adult NDO, a more recent integrative review has indicated that the information provided is still too limited for clinicians to be able to match trial data to the needs of individual patients with SCI, mainly due to the lack of use of standardised clinical evaluation tools such as the American Spinal Injury Association bladder diary and validated symptoms score [186, 189].

Higher doses or a combination of antimuscarinic agents may be an option to maximise outcomes in neurological patients [182, 183, 190-193]. However, these drugs have a high incidence of adverse events, which may lead to early discontinuation of therapy. Despite this, NDO patients have generally shown better treatment adherence compared to idiopathic DO patients [194].

Choice of antimuscarinic agent: Oxybutynin [134, 182, 183, 185, 186, 195], trospium [186, 192, 196], tolterodine [197] and propiverine [186, 198] are established, effective and well-tolerated treatments even in long-term use [185, 186, 199, 200]. Darifenacin [201, 202] and solifenacin [203] have been evaluated in NDO secondary to SCI and MS [186, 201-203] with results similar to other antimuscarinic drugs. A pilot study using solifenacin in NDO due to PD showed an improvement in UI [204]. Fesoterodine, an active metabolite of tolterodine, has also been introduced; improving urodynamic variables in SCI, MS and PD patients [205, 206]. Fesoterodine for SCI patients can diminish the magnitude and frequency of AD episodes [207]. Favourable results with the new drug imidafenacin have been reported in suprapontine as well as SCI patients [208, 209].

Side effects: Controlled-release antimuscarinics have some minor side effects, e.g. dry mouth [210]. It has been suggested that different ways of administration may help to reduce side effects [211]. Imidafenacine has been safely used in neurological patients with no worsening of cognitive function [208]. Nevertheless, the potential risk of developing dementia should be taken into account [212]; consider switching to beta-3 agonists or other therapies if cognition is affected [213].

Beta-3-adrenergic receptor agonists
Despite the increasing use of mirabegron in neuro urological patients, its role in these patients is still unclear [214, 215]. In MS and SCI patients, with very short follow-up, mirabegron has not demonstrated any significant effect on detrusor pressure or cystometric capacity [69, 216, 217], despite the reported improvement in LUT symptoms and quality of life similar to antimuscarinics [215]. Cardiovascular safety in NDO population has been suggested in a placebo-controlled RCT [218]. A significant subjective improvement in NDO symptoms has also been reported using lower dosages of mirabegron in patients affected by CNS lesions without any negative effects on voiding function [219]. A standard dosage of 50 mg has been found effective with no worsening of cognitive function in patients with PD [220].

Vibegron treatments significantly improved maximum cystometric capacity, bladder compliance, and NDO in a retrospective cohort study [221], but more studies are needed to do a recommendation.

Other drugs
A SR found that desmopressin may be effective for treating nocturnal polyuria in MS patients; however, adverse events were common, with the included studies being heterogeneous and of low quality [222].

Combination therapy with mirabegron and desmopressin in MS patients has shown promising results; however, clinical experience is still very limited in neuro-urological populations [223, 224].

In preliminary studies, improvements in daily incontinence rates, nocturia, daytime and 24-hour voids, as well as the low risk of adverse events, suggest that cannabinoids may be effective and safe in MS patients [225, 226]. A concomitant improvement in NDO symptoms has been reported in male MS patients using daily tadalafil to treat neurogenic erectile dysfunction (ED) [227].

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 [228]. Only preclinical studies have documented the potential benefits of cannabinoid agonists for improving detrusor contractility when administered intravesically [229, 230].

Decreasing bladder outlet resistance: α-blockers (e.g. tamsulosin, naftopidil and silodosin) seem to be effective for decreasing bladder outlet resistance, PVR and AD [231-235].

Increasing bladder outlet resistance: Several drugs have shown efficacy in selected cases of mild SUI, but there are no high-level evidence studies in neurological patients [134].

3.4.2.4 Summary of evidence and recommendations for drug treatments

Summary of evidence	**LE**
Long-term efficacy and safety of antimuscarinic therapy for NDO is well documented.	1a
Mirabegron has shown similar symptom related clinical effects compared to antimuscarinics.	1b
Mirabegron does not improve urodynamic parameters in NDO patients.	1a
Maximise outcomes for NDO by considering combination therapy	3

Recommendations	Strength rating
Use antimuscarinic therapy as the first-line medical treatment for neurogenic detrusor overactivity.	Strong
Do not use mirabegron with the intention of reducing urodynamically proven neurogenic detrusor overactivity.	Strong
Prescribe α-blockers to decrease bladder outlet resistance.	Strong
Do not prescribe parasympathomimetics for underactive detrusor.	Strong

3.4.2.5 Minimally invasive treatment

3.4.2.5.1 Catheterisation

Intermittent self- or third-party catheterisation [236, 237] is the preferred management for neuro-urological patients who cannot effectively empty their bladders [134]. An adequate hand function is an independent risk factor for cessation of intermittent catheterisation (IC) [238].

It has not yet been established whether or not the incidence of UTI, other complications and user satisfaction are affected by either sterile, aseptic or clean IC, coated or uncoated catheters or by any other catheter type [239].

Sterile IC cannot be considered a routine procedure [134, 240] and careful counselling should be employed before commencing IC. In those with MS, commencing IC increases UTI rate over one year by seven fold, without improvement in QoL or symptom score [241]. In addition, in those with SCI, dissatisfaction (and discontinuation) is associated with increased UTI frequency, as well as being of the female sex [242]. It is worth considering patient satisfaction and subsequent compliance when instigating and continuing IC. Shared decision making is imperative, as although IC has better medical outcomes than indwelling catheterisation, in the SCI population it is associated with worse reported QoL compared to indwelling catheters, especially if recurrent (> 4 per year) UTIs complicate management [61, 243]. The use of hydrophilic catheters is associated with a lower rate of UTI [244]. An observational study found that of the 56.9% of patients who used IC 42.1% of patients discontinued IC within 12 months with inconvenience (36%), leakage (20%) and increased infections (19%) listed as the main reasons for the discontinuation [243].

To minimise the risk of UTI in neuro-urological patients, it is important that patient should be adequately taught to self-catheterise [134, 245-249]. The average frequency of catheterisations per day is four to six times [250] and the catheter size most often used is between 12-16 Fr. In aseptic IC, an optimum frequency of five times showed a reduction of UTI [250]. 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 [134, 251-258]; therefore, both procedures should be avoided, when possible. Silicone catheters are preferred as they are less susceptible to encrustation and because of the high incidence of latex allergy in the neuro-urological patient population [259].

Bladder cancer might be an increased risk in the general population with an indwelling catheter including neuro-urological patients, and clinicians should promptly investigate patients with the standard red flags for bladder cancer [258, 260].

3.4.2.5.2 Summary of evidence and recommendations for catheterisation

Summary of evidence	LE
Intermittent catheterisation is the standard treatment for patients who are unable to empty their bladder.	3
Indwelling transurethral catheterisation and suprapubic cystostomy are associated with a range of complications as well as an enhanced risk for UTI.	3

Recommendations	Strength rating
Use intermittent catheterisation as a standard treatment for patients who are unable to empty their bladder.	Strong
Thoroughly instruct patients in the technique and risks of intermittent catheterisation.	Strong
Avoid indwelling transurethral and suprapubic catheterisation whenever possible.	Strong

3.4.2.5.3 Intravesical drug treatment

To reduce NDO, antimuscarinics can also be administered intravesically [261]. The efficacy and tolerability of intravesical administration of oxybutynin hydrochloride for treatment of NDO has been demonstrated in a recent randomised controlled study [211]. This approach may reduce adverse effects due to the fact that the antimuscarinic drug is metabolised differently [262] and a greater amount is sequestered in the bladder, even more than with electromotive administration [263].

The vanilloids, capsaicin and resiniferatoxin, desensitise the C-fibres for a period of a few months [264, 265]. Clinical studies have shown that resiniferatoxin has limited clinical efficacy compared to botulinum toxin A injections in the detrusor [264].

Although preliminary data suggest that intravesical vanilloids might be effective for treating neurological LUT dysfunction, their safety profile appears to be unfavourable [222]. Currently, there is no indication for the use of these substances, which are not licensed for intravesical treatment.

3.4.2.5.4 Summary of evidence and recommendations for intravesical drug treatment

Summary of evidence	**LE**
A significant reduction in adverse events was observed for intravesical administration of oxybutynin compared to oral administration.	1a

Recommendation	**Strength rating**
Offer intravesical oxybutynin to neurogenic detrusor overactivity patients with poor tolerance to the oral route.	Strong

3.4.2.5.5 Botulinum toxin injections in the bladder

Botulinum toxin A causes a long-lasting but reversible chemical denervation that lasts for about nine months [266, 267]. The toxin injections are mapped over the detrusor in a dosage that depends on the preparation used. Botulinum toxin A has been proven effective in patients with neuro-urological disorders due to MS, SCI and PD in multiple RCTs and meta-analyses [268-271]. In mid- to long-term follow-up, 50%-70% of the patients continue botulinum toxin treatment [272-274]. Urodynamic studies might be necessary after treatment in order to monitor the effect of the injections on bladder pressure [275]. Repeated injections seem to be possible without loss of efficacy, even after initial low response rates, based on years of follow-up [266, 276-279]. The clinical efficacy of botulinum toxin A injection in patients with low morbidity after failure of augmentation enterocystoplasty has been demonstrated [280, 281]. The effectiveness of the different toxin variations seems to be comparable [282, 283]. A switch between different toxin variations may improve responsiveness [284]. The most frequent side effects are UTIs, urinary retention and haematuria [285]. Intermittent catheterisation may become necessary, this is especially relevant in MS patients as they do not often perform IC prior to intravesical botulinum toxin injections. However, a lower dose of botulinum toxin A (100 U) may reduce the rate of IC in MS patients [286]. Rare complications include generalised muscle weakness and AD [285]. Including the trigone has been suggested to be more effective than trigone-sparing injection [287]. Current research focuses on different delivery approaches to injection such as liposome encapsulated botulinum toxin to decrease side effects [288]. Neuro-urological patients with an indwelling catheter and concomitant bladder pain and/or catheter bypass leakage could benefit from intravesical botulinum injections [289].

3.4.2.5.6 Bladder neck and urethral procedures

Reduction of the bladder outlet resistance: This 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 – Section 3.4.3.1). However, high rates of long-term complications are still noted after the procedures. Patients should be fully aware about the high risk of urinary incontinence which can be the main reason of dissatisfaction although its management with external devices [290] (Section 3.4.2.1).

- *Botulinum toxin A:* This can be used to treat DSD effectively by injecting the sphincter at a dose that depends on the preparation used. An improvement of patient reported outcomes has been described in DSD patients with cervical, incomplete SCI, detrusor overactivity and partial hand function [291]. Detrusor sphincter dyssynergia is abolished only for a few months, necessitating repeat injections. The benefit of this treatment has been reported to be limited with mild AEs [292]. However, a recent SR concluded that, because of limited evidence, future RCTs assessing the effectiveness of botulinum toxin A injections also need to address the uncertainty about the optimal dose and mode of injection [293]. In addition, this therapy is not licensed.

- *Increasing bladder outlet resistance:* This can improve the continence condition. However, despite early positive results with urethral bulking agents, a relative early loss of continence is reported in patients with neuro-urological disorders [134, 294, 295].

- *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 [296].

3.4.2.5.7 Summary of evidence and recommendations for botulinum toxin A injections

Summary of evidence	**LE**
Botulinum toxin A has been proven effective in patients with neuro-urological disorders due to MS or SCI in multiple RCTs and meta-analyses.	1a

Recommendations	**Strength rating**
Use botulinum toxin injection in the detrusor to reduce neurogenic detrusor overactivity in multiple sclerosis or spinal cord injury patients if antimuscarinic therapy is ineffective.	Strong

*3.4.3 **Surgical treatment***

There is considerable heterogeneity in outcome parameters and definitions of cure used to report on outcomes of surgical interventions for SUI in neuro-urological patients [297]. The heterogeneity of outcome reporting makes it difficult to interpret and compare different studies and therapies. A consistent comparison of the outcomes of therapy can only be made after standardisation of outcome parameters and definitions of cure or success; therefore, it would seem prudent to develop a core outcome set (COS) for use in UI research in neuro-urological patients [297]. Until such a COS is developed it would seem feasible to use both a subjective and objective outcome parameter and the combination of both to define cure [297]. Due to the importance of QoL for neuro-urological patients a disease-specific QoL questionnaire or a validated bother questionnaire validated for neuro-urological patients should be used as the subjective outcome parameter [297].

3.4.3.1 Bladder neck and urethral procedures to improve neurogenic stress urinary incontinence

Procedures to treat neurogenic stress urinary incontinence (N-SUI) are suitable only when the risk for upper urinary tract deterioration and detrusor pressures can be controlled. A simultaneous therapy of bladder management may be necessary [298].

- *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 [298-303]. There is growing evidence that female synthetic mid-urethral slings (MUS) can be used effectively with acceptable medium to long-term results and minimal morbidity in neuro-urological patients [300, 301]. Autologous pubovaginal sling has been considered the procedure of choice for treating female N-SUI and it should be preferred when concomitant bladder augmentation is also indicated [300]. Compared to transobturator, the retropubic route has been suggested to be more effective in women with N-SUI [301]. However, either for both synthetic MUS as well as autologous sling additional bladder management may become necessary due to the risk of "*de novo*" LUTS [300-302]. Complications include the need to perform IC especially after retropubic approach, mesh erosion or extrusion requiring partial or total removal, and retropubic haematoma and the 5-year failure rate is relevant [300, 301]. In men, both autologous and synthetic slings have been investigated less frequently compared to women and mainly in patients already on IC regimen before surgery [300]. The cure rate ranged from 29% to 71% at a follow-up of 12 to 36 months. Complications included haematoma, tape infection or erosion into urethra and difficulty to perform IC [300].

- *Artificial urinary sphincter (AUS):* This device was introduced by Light and Scott for male patients with N-SUI [304]. It has stood the test of time and acceptable long-term outcomes can be obtained [305]. Implantation of AUS is the most often performed procedure for N-SUI especially in men with a high success/improvement rate [300]. However, the complication and re-operation rates are higher than in non-neurogenic SUI (up to 60%), so it is advisable that patients are conscientiously informed about the success rates as well as the possible need for re-intervention [306, 307]. In a case series with 25 years follow-up only 7.1% of patients were revision free at twenty years [308]. Re-interventions are commonly due to mechanical failure, urethral atrophy or erosion and infection. There is growing interest in the use of this device with development of laparoscopic and robot-assisted approaches via an anterior or a posterior access to the bladder neck [309, 310]. Nonetheless, careful patient selection and appropriate preoperative investigation are crucial [310]. Although from a single institution series, long-term surgical results are now available and support the potentially prominent role of AUS placement in female patients with N-SUI [300, 311-313]. Long-term surgical and patient-reported outcomes are needed to determine the role of AUS placement in female patients with N-SUI [311].

- *Adjustable continence device – (inflatable balloons):* The efficacy of this device has been reported mainly in post-prostatectomy incontinence (non-neurogenic male lower urinary tract symptoms EAU guidelines – Section 5.6.5.3.2). A similar cure and improvement rate has been reported in neurological patients when compared to non-neurological patients [314, 315]. However, it is associated with a low safety profile due to the high complication and limited device survival rate [316].

- *Bladder neck and urethra reconstruction:* The classical Young-Dees-Leadbetter procedure [317] for bladder neck reconstruction in children with bladder exstrophy, and Kropp urethra lengthening [318] improved by Salle [319], are established methods to restore continence provided that IC is practiced and/or bladder augmentation is performed [134, 320].

Endoscopic techniques for treating anatomic bladder outlet obstruction [321]:

- *Transurethral resection of the prostate* is indicated in male patients with refractory LUT symptoms due to benign prostatic obstruction. Special consideration should be given to pre-operative abnormal sphincter function and the type of neurological disease, which can lead to persistent or "*de novo*" LUTS [322, 323].

- *Urethrotomy* is indicated in patients with urethral strictures. Cold knife or neodymium:YAG contact laser urethrotomy at the twelve o'clock position can be performed [324, 325].

- *Urethroplasty* should be performed on an individual basis depending on the urethral lesion (erosion, stricture, diverticula, fistula), length and location. However urethral surgery in neurological patients has a high failure rate and in recurrent strictures, urinary diversion should be considered [326].

- *Sphincterotomy* has been shown to be an efficient technique for the resolution of AD, hydronephrosis and recurrent UTI, and for decreasing detrusor pressure, PVR and vesicoureteral reflux. It is irreversible and should be limited to men who are able to wear a condom catheter. By staged incision, bladder outlet resistance can be reduced without completely losing the closure function of the urethra [133, 134, 327]. The incision with less complications, is the twelve o'clock sphincterotomy with cold knife [328] or neodymium:YAG laser [329]. Sphincterotomy needs to be repeated at regular intervals in many patients [330], but it is efficient and does not cause severe adverse effects [133, 331]. Secondary narrowing of the bladder neck may occur, for which combined bladder neck incision might be considered [332].

- *Bladder neck incision:* This may be indicated for anatomical or functional bladder neck obstruction [290, 293, 321, 323].

- *Stents:* Implantation of urethral stents results in continence being dependent on adequate closure of the bladder neck [134]. The results are comparable with sphincterotomy and the stenting procedure has a shorter duration of surgery and hospital stay [333, 334]. However, the costs [133], possible complications and re-interventions [335, 336] are limiting factors in their use [337-340].

3.4.3.2 Denervation, deafferentation, sacral neuromodulation

Sacral anterior root stimulation (SARS) is aimed at producing detrusor contraction. The technique was developed by Brindley [341] and is only applicable to complete lesions above the implant location, as its stimulation amplitude is over the pain threshold. The urethral sphincter efferents are also stimulated, but because the striated muscle relaxes faster than the smooth muscle of the detrusor, so-called "post-stimulus voiding" occurs. This approach has been successful in highly selected patients [342-345]. Although it has been shown that detrusor pressure during SARS decreases over time, the changes do not seem to be clinically relevant during the first decade after surgery [346]. By changing the stimulation parameters, this method can also induce defecation or erection. A recent study reported that Charcot spinal arthropathy should be considered as a potential long-term complication of SARS, leading to spinal instability and to SARS dysfunction [347].

Sacral rhizotomy, also known as sacral deafferentation, has achieved some success in reducing NDO [348-350], but nowadays, it is used mostly as an adjuvant to SARS [342, 351-354]. Alternatives to rhizotomy are sought in this treatment combination [355-357].

There is growing evidence, including one RCT [358], on the use of sacral neuromodulation for treating neuro-urological symptoms, but due to the paucity of disease specific studies it remains unclear which neurological patients are most suitable [359-361]. MS patients with NDO have been often reported as good responders to several types of neuromodulations [361-363]. The neuromodulation effect on urodynamic parameters is still unclear [364]. With the development of MRI-compatible pulse generators and leads, the avoidance of this procedure in patients needing this imaging technique for their follow-up is no longer required.

Other neuromodulation techniques like the deep brain stimulation in PD patients may have beneficial effects in the LUT but these depend on the site of stimulation and although prospective, specifically designed studies are needed in neuro-urological patients [365, 366].

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 [367] and latissimus dorsi [368] have been used successfully in neuro-urological patients [369, 370].

3.4.3.4 Bladder augmentation

The aim of auto-augmentation (detrusor myectomy) is to reduce NDO or improve 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 [133, 298, 371-374].

Replacing or expanding the bladder by intestine ensures a low-pressure reservoir improving bladder compliance and abolishing or at least reducing NDO [375, 376]. Improved QoL and stable renal function has been reported during long-term follow-up in SCI and SB patients [377-379]. It is not clear whether augmented cystoplasty should be combined with simultaneous ureter reimplantation when high grade VUR is present [379, 380]. Patients performing IC with augmented cystoplasty had better urinary function and satisfaction with their urinary symptoms compared to patients performing IC with or without botulinum toxin treatment [381]. Long-term complications includes bladder perforation (1.9%), mucus production (12.5%), metabolic abnormalities (3.35%), bowel dysfunction (15%), and stone formation (10%) [377].

The procedure should be used with caution in neuro-urological patients but may become necessary if all less-invasive treatment methods have failed. Special attention should be paid to patients with pre-operative renal scars since metabolic acidosis can develop [382]. Supratrigonal cystectomy [376, 383], is indicated in patients with a severely thick and fibrotic bladder wall. Intermittent catheterisation may become necessary after this procedure. The long-term scientific evidence shows that bladder augmentation is a highly successful procedure that stabilises renal function and prevents anatomical deterioration; however, lifelong follow-up is essential in this patient group given the significant morbidity associated with this procedure [377, 384, 385].

3.4.3.5 Urinary diversion

When no other therapy is successful, urinary diversion must be considered for the protection of the UUT [298].

Continent diversion: This should be the first choice for urinary diversion. Patients with limited dexterity or anatomical barriers (e.g., urethral strictures, women with poor mobility and/or obesity) may prefer a stoma instead of using the urethra for catheterisation. For cosmetic reasons, the umbilicus is often used for the stoma site [386-392]. A SR of the literature concluded that continent catheterisable tubes/stomas are an effective treatment option in neuro-urological patients unable to perform intermittent self-catheterisation through the urethra [393]. The positive impact on QoL comprised sexual life improvement, better body image, high satisfaction rates in urologic management, independence, time saved on catheterisation, and better capacity to perform daily activity and work [394]. However, the complication rates were significant with 85/213 post-

operative events requiring re-operation [393]. Tube stenosis occurred in 4-32% of the cases. Complications related to concomitant procedures (augmentation cystoplasty, pouch) included neovesicocutaneous fistulae (3.4%), bladder stones (20-25%), and bladder perforations (up to 40% in one case series) [393].

Incontinent diversion: If catheterisation is impossible, incontinent diversion with a urine-collecting device is indicated. Ultimately, it could be considered in selected patients with intractable and untreatable incontinence, in patients with LUT destruction, when the UUT is severely compromised, and in patients who refuse other therapy [134]. An ileal segment is used for the diversion in most cases [134, 395-398]. Patients gain better functional status and QoL after surgery [399]. Moreover, to achieve a high satisfaction rate, it is necessary to involve relatives and caregivers with stoma management. Concomitant cystectomy to avoid pyocystitis may be advisable [400]. All procedures can be done open, laparoscopically as well as robotically [401-403]. However, prospective comparative studies are lacking [402, 404].

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 [134]. The patient must be carefully counselled and must comply meticulously with the instructions [134]. Successful undiversion can then be performed [405].

In a prospective observational study (n=1,479), QoL was investigated in neuro-urological patients using four different bladder management options. It is the first study to focus on PROMS and noted that surgery was associated with fewer bladder management difficulties and a better QoL [61].

3.4.3.6 Summary of evidence and recommendations for surgical treatment

Summary of evidence	**LE**
Bladder augmentation is an effective option to decrease detrusor pressure and increase bladder capacity, when all less-invasive treatment methods have failed.	3
Urethral sling placement is an established procedure, with acceptable mid- to long-term results, in women with the ability to self-catheterise.	3
Artificial urinary sphincter insertion is the most frequently offered option to treat neurogenic SUI with acceptable long-term outcomes, in males. The complication and re-operation rates are higher in neuro-urological patients; therefore, patients must be adequately informed regarding the success rates as well as the complications that may occur following the procedure.	3
Sacral neuromodulation is an effective and safe option in the treatment of selective neurogenic LUT dysfunction.	1b

Recommendations	**Strength rating**
Offer bladder augmentation in low bladder compliance and/or refractory neurogenic detrusor overactivity.	Strong
Place an autologous urethral sling as first-line treatment in female patients with neurogenic stress urinary incontinence (SUI) who are able to self-catheterise.	Strong
Place a synthetic urethral sling, as an alternative to autologous urethral slings, in selected female patients with neurogenic SUI who are able to self-catheterise.	Weak
Insert an artificial urinary sphincter in selected female patients with neurogenic SUI; however, patients should be referred to experienced centres for the procedure.	Weak
Insert an artificial urinary sphincter in male patients with neurogenic SUI.	Strong
Consider sacral neuromodulation in selected neuro-urological patients.	Strong

3.5 Urinary tract infection in neuro-urological patients

3.5.1 Epidemiology, aetiology and pathophysiology

Urinary tract infection is the onset of signs and/or symptoms accompanied by laboratory findings of a UTI (bacteriuria, leukocyturia and positive urine culture) [387]. There are no evidence-based cut-off values for the quantification of these findings [406]. The published consensus is that a significant bacteriuria in persons performing IC is present with > 102 cfu/mL, > 104 cfu/mL in clean-void specimens and any detectable concentration in suprapubic aspirates. Regarding leukocyturia, ten or more leukocytes in centrifuged urine samples per microscopic field (400x) are regarded as significant [387].

The pathogenesis of UTI in neuro-urological patients is multifactorial. Male gender seems to be a risk factor for febrile and recurrent UTIs [407, 408]. Several etiological factors have been described: altered intrinsic defence mechanisms, impaired washout and catheterisation [409-412]. Poor glycemic control has also been established as a risk factor for UTI in women with type 1 diabetes [413]. However, the exact working mechanisms 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% [414]. Sphincterotomy and condom catheter drainage has a 57% prevalence [415]. Asymptomatic bacteria should not be routinely screened for in this population [416] but a nomogram can be a helpful tool for early prediction of UTIs [417].

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 [418]. Other problems, such as AD, may develop or worsen due to a UTI [244]. The most common signs and symptoms suspicious of a UTI in those with neuro-urological disorders are fever, new onset or increase in incontinence, including leaking around an indwelling catheter, increased spasticity, malaise, lethargy or sense of unease, cloudy urine with increased urine odour, discomfort or pain over the kidney or bladder, dysuria, or AD [244, 419]. New incontinence is the most specific symptom, whereas cloudy and foul-smelling urine has the highest positive predictive value for UTI diagnosis [420].

*3.5.2 **Diagnostic evaluation***

Urine culture and urinalysis are the optimum tests for the diagnosis of UTI in neuro-urological patients. A dipstick test is more useful to exclude rather than to prove UTI [421, 422] and is not recommended. As bacterial strains and resistance patterns in persons with neuro-urological disorders may differ from those of able-bodied patients, microbiologic testing is mandatory [423].ro-urological disorders may differ from those of able-bodied patients, microbiologic testing is mandatory [400].

*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 [424]. Urinary tract infections in persons with neuro-urological disorders are by definition a complicated UTI; therefore, single-dose treatment is not advised. There is no consensus in the literature about the duration of treatment as it depends on the severity of the UTI and the involvement of the kidneys and the prostate. Generally, a five to seven day course of antibiotic treatment is advised, which can be extended up to fourteen days according to the extent of the infection [424]. The choice of antibiotic therapy should be based on the results of the microbiologic testing. If immediate treatment is mandatory (e.g., fever, septicaemia, intolerable clinical symptoms, extensive AD), the choice of treatment should be based on local and individual resistance profiles, as well as on results from previous urine cultures [425]. In patients with afebrile UTI, an initial non-antibiotic treatment may be justified [426, 427].

3.5.3.1 Recurrent UTI

Recurrent UTI in patients with neuro-urological disorders may indicate suboptimal management of the underlying functional problem, e.g., high bladder pressure during storage and voiding, incomplete voiding or bladder stones. The improvement of bladder function, by treating NDO by botulinum toxin A injection in the detrusor [428], and the removal of bladder stones or other direct supporting factors, especially indwelling catheters, as early as possible, are mandatory [423].

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. In a meta-analysis the use of hydrophilic catheters was associated with a lower rate of UTI [244].

Various medical approaches have been tested for UTI prophylaxis in patients with neuro-urological disorders. The benefit of cranberry juice or probiotics for the prevention of UTI could not be demonstrated in RCTs [429, 430]. Methenamine hippurate is not effective in individuals with neuro-urological symptoms [431]. There is no sufficient evidence to support the use of L-methionine for urine acidification to prevent recurrent UTIs [432]. There is only weak evidence that oral immunotherapy reduces bacteriuria in patients with SCI [433] and that recurrent UTIs are reduced [434]. Low-dose, long-term, antibiotic prophylaxis can reduce UTI frequency, but increases bacterial resistance and is therefore not recommended [435].

Weekly cycling of antibiotic prophylaxis provided long-term positive results, but the results of this trial need to be confirmed in further studies [436]. 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 [437], cannot be recommended as a treatment option. There is initial evidence that homeopathic treatment can decrease UTI frequency [438].

The use of daily intravesical iodine washouts shows promising results for reduction of symptomatic UTIs and hospitalisation without increase in multi drug resistance in patients with NLUTD who perform IC [439] Other intravesical agents have also been trialed for the reduction of UTIs, both antimicrobial and non. Intravesical gentamicin has been shown to reduce UTIs and oral antibiotic use, without increasing antimicrobial resistance [435, 440]. Intravesical hyaluronic acid was also reported in this metanalysis to reduce mean number of UTIs [441].

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 [442]. Prevention of UTIs 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 **Summary of evidence and recommendations for the treatment of UTI***

Summary of evidence	**LE**
Treatment of asymptomatic bacteriuria results in significantly more resistant bacterial strains without improving patient outcome.	1a
Low-dose, long-term, antibiotic prophylaxis can reduce UTI frequency, but increases bacterial resistance.	2a
Recurrent UTIs in patients with neuro-urological disorders may indicate suboptimal management of the underlying functional problem. Improvement of bladder function as early as possible is mandatory.	3
There is currently no preventive measure for recurrent UTI in patients with neuro-urological disorders that can be recommended without limitations.	3

Recommendations	**Strength rating**
Do not use dipstick urine analysis to screen for urinary tract infection (UTI) in neuro-urological patients.	Strong
Do not screen for or treat asymptomatic bacteriuria in patients with neuro-urological disorders.	Strong
Avoid the use of long-term antibiotics for recurrent UTIs.	Strong
In patients with recurrent UTIs, optimise treatment of neuro-urological symptoms and remove foreign bodies (e.g., stones, indwelling catheters) from the urinary tract.	Strong
Individualise UTI prophylaxis in patients with neuro-urological disorders as there is no optimal prophylactic measure available.	Strong

3.6 Sexual function and fertility

This section specifically focuses on sexual dysfunction and infertility in patients with a neurological disease [443, 444]. Non-neurogenic, male sexual dysfunction and infertility are covered in separate EAU Guidelines [445, 446]. 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 [447]. Adopting a systematic approach, such as the PLISSIT model (Permission, Limited Information, Specific Suggestions and Intensive Therapy) [448], provides a framework for counselling and treatment involving a stepwise approach to the management of neurogenic sexual dysfunction. Sexual dysfunction is associated with neurogenic LUT dysfunction in patients with MS [449] and SB [450]. Although various PROMs are available to evaluate sexual function, the evidence for good PROMs is limited and studies with high methodological quality are needed [77].

3.6.1 ***Erectile dysfunction***

3.6.1.1 Phosphodiesterase type 5 inhibitors (PDE5Is)

Phosphodiesterase type 5 inhibitors (PDE5Is) are recommended as first-line treatment in neurogenic ED [443, 444]. In SCI patients, tadalafil, vardenafil and sildenafil have all improved retrograde ejaculation and improved erectile function and satisfaction on IIEF-15. Tadalafil 10 mg was shown to be more effective than sildenafil 50 mg. All currently available PDE5Is appear to be effective and safe, although there are no high-level evidence studies in neuro-urological patients investigating the efficacy and side effects across different PDE5Is, dosages and formulations [451].

For MS patients two studies reported significant improvement in ED when using sildenafil and tadalafil [444, 452] however, another study showed no improvement in ED with sildenafil [453]. One study found a significant improvement in ED in SB patients when using sildenafil [454].

In PD normal erectile function was described in over half of the patients using sildenafil 100 mg and a significant improvement in IIEF-15 score was found compared to placebo. While most neuro-urological patients require long-term therapy for ED some have a low compliance rate or stop therapy because of side effects [455, 456], most commonly headache and flushing [444]. In addition, PDE5Is may induce relevant hypotension in patients with tetraplegia/high-level paraplegia and multiple system atrophy [455, 456]. As a prerequisite for successful PDE5I-therapy, some residual nerve function is required to induce erection. Since many patients with SCI use on-demand nitrates for the treatment of AD, they must be counselled that PDE5Is are contraindicated when using nitrate medication.

3.6.1.2 Drug therapy other than PDE5Is

Fampridine to treat neurogenic spasticity has been shown to be beneficial in improving ED in two domains of the IIEF-15 in SCI and MS patients, however, with a significant discontinuation rate due to severe adverse events [457]. Sublingual apomorfine was shown to have poor results on ED in SCI patients and side-effects in half of the patients [458]. In PD, pergolide mesylate showed a significant improvement in IIEF-15 scores up to twelve months follow-up [459].

3.6.1.3 Mechanical devices

Mechanical devices (vacuum tumescence devices and penile rings) may be effective but are less popular [460-464].

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 [465-471], 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 [455]. Intra-urethral alprostadil application is an alternative, but less effective, route of administration [467, 472].

3.6.1.5 Sacral neuromodulation

Sacral neuromodulation for LUT dysfunction may improve sexual function; however, high level evidence studies are lacking.

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 [444]. Serious complications, including infection and prosthesis perforation, may occur in about 10% of patients, depending on implant type [473-475].

3.6.1.7 Summary of evidence and recommendations for erectile dysfunction

Summary of evidence	LE
The long-term efficacy and safety of oral PDE5Is for the treatment of ED is well documented.	1b
Intracavernous vasoactive drug injections have been shown to be effective in a number of neurological conditions, including SCI and MS; however, their use requires careful dose titration and precautions.	3
Mechanical devices (vacuum tumescence devices and penile rings) may be effective but are less popular.	3
Reserve penile prostheses for selected patients, those in which all conservative treatments have failed, with neurogenic ED.	4

Recommendations	Strength rating
Prescribe oral phosphodiesterase type 5 inhibitors as first-line medical treatment in neurogenic erectile dysfunction (ED).	Strong
Give intracavernous injections of vasoactive drugs (alone or in combination) as second-line medical treatment in neurogenic ED.	Strong
Offer mechanical devices such as vacuum devices and rings to patients with neurogenic ED.	Strong

*3.6.2 **Male fertility***

Male fertility can be compromised in the neurological patient by ED, ejaculation disorder, impaired sperm quality or various combinations of these three disorders. Among the major conditions contributing to neurogenic infertility are pelvic and retroperitoneal surgery, diabetes mellitus, SB, MS and SCI [476]. Erectile dysfunction is managed as described previously. Retrograde ejaculation may be reversed by sympathomimetic agents contracting the bladder neck, including imipramine, ephedrine, pseudoephedrine, and phenylpropanolamine [476]. The use of a balloon catheter to obstruct the bladder neck may be effective in obtaining antegrade ejaculation [477]. If antegrade ejaculation is not achieved, the harvest of semen from the urine may be considered [478].

Prostatic massage is safe and easy to use for obtaining semen in men with lesions above Th 10 [479]. In several patients, vibrostimulation or transrectal electroejaculation are needed for sperm retrieval [476, 480, 481]. Semen retrieval is more likely with vibrostimulation in men with lesions above Th 10 [482-484]. In men with SCI, especially at or above Th 6, AD might occur during sexual activity and ejaculation [485, 486]; 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 [487].

In men with MS, use of disease modifying drugs during the conception phase, has not been associated with altered pregnancy outcomes [488]. Surgical procedures, such as, microsurgical epididymal sperm aspiration or testicular sperm extraction, may be used if vibrostimulation and electroejaculation are not successful [489, 490]. Pregnancy rates in patients with SCI are lower than in the general population, but since the introduction of intracytoplasmic sperm injection, men with SCI now have a good chance of becoming biological fathers [491-493].

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 [494];
- in SCI patients sperm quality decreases at the early post-traumatic phase demonstrating lower spermatozoid vitality (necrospermia), reduced motility (asthenospermia) and leucospermia [489];
- long-term valproate treatment for epilepsy negatively influences sperm count and motility [495];
- vibrostimulation produces samples with better sperm motility than electrostimulation [496, 497];
- electro-ejaculation with interrupted current produces better sperm motility than continuous current [498];
- freezing of sperm is unlikely to improve fertility rates in men with SCI [499].

3.6.2.2 Summary of evidence and recommendations for male fertility

Summary of evidence	LE
Vibrostimulation and transrectal electroejaculation have been shown to be effective for sperm retrieval in neuro-urological patients.	1b
Surgical procedures, such as, microsurgical epididymal sperm aspiration or testicular sperm extraction, may be used if vibrostimulation and electroejaculation are not successful.	3
In men with SCI at or above Th 6, AD might occur during sexual activity and ejaculation.	3

Recommendations	Strength rating
Perform vibrostimulation and transrectal electroejaculation for sperm retrieval in men with spinal cord injury.	Strong
Perform microsurgical epididymal sperm aspiration, testicular sperm extraction and intracytoplasmic sperm injection after failed vibrostimulation and/or transrectal electroejaculation in men with spinal cord injury.	Strong
Counsel men with spinal cord injury at or above Th 6 and fertility clinics about the potentially life-threatening condition of autonomic dysreflexia.	Strong

3.6.3 Female sexuality

The most relevant publications on neurogenic female sexual dysfunction are in women with SCI and MS, while there is only limited evidence for women with stroke and SB. 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 [500-502]. Although sexual dysfunction is very common in women with MS, it is still often overlooked by medical professionals [503, 504]. A vast majority of female SB patients showed sexual dysfunction [505] and considered information about sexuality from their physicians insufficient [506]. 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 [507-509]. Similarly, majority of female stroke patients are not sexually satisfied [510].

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 [500, 511-513].

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 [444]. Although good evidence exists that psychological interventions are effective in the treatment of female hypoactive sexual desire disorder and female orgasmic disorder [514], there is a lack of high-level evidence 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 are 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 [507, 515, 516].

Sacral neuromodulation for LUT dysfunction may improve sexual function but high-evidence studies are lacking [444].

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 [517].

Although it seems that the reproductive capacity of women with SCI is only temporarily affected by SCI with cessation of menstruation for approximately six months after SCI [518], there are no high-level evidence 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 [519].

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 [520-524]. Obstetric outcomes include higher rates of Caesarean sections and an increased incidence of low birth-weight babies [519, 522-524].

Epidural anaesthesia is chosen and effective for most patients with AD during labour and delivery [525, 526].

There is very little published data on women's experience of the menopause following SCI [527]. Women with MS who plan a pregnancy should evaluate their current drug treatment with their treating physician [528-530]. Clinical management should be individualised to optimise both the mother's reproductive outcomes and MS course [528, 529, 531].

3.6.4.1 Summary of evidence and recommendation for female sexuality and fertility

Summary of evidence	**LE**
Data on specific drugs for treating female sexual dysfunction are poor and controversial.	4
There are limited numbers of studies on female fertility in neurological patients, clinical management should be individualised to optimise both the mother's reproductive outcomes and medical condition.	4

Recommendations	**Strength rating**
Do not offer medical therapy for the treatment of neurogenic sexual dysfunction in women.	Strong
Take a multidisciplinary approach, tailored to individual patient's needs and preferences, in the management of fertility, pregnancy and delivery in women with neurological diseases.	Strong

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 to assess the UUT [132].

Depending on the type of the underlying neurological pathology and the current stability of the neuro-urological symptoms, the interval between initial investigations and control diagnostics may vary and, in many cases, should not exceed one to two years. high-risk neuro-urological this interval should be much shorter. The UUT should be checked by ultrasonography at regular intervals in high-risk patients; about once every six months [6, 532]. In these patients, physical examination and urine laboratory should take place every year [6, 532]. In MS patients higher scores on the Expanded Disability Status Scale (EDSS) are associated with risk factors for UUT deterioration [533]. A urodynamic investigation should be performed as a diagnostic baseline, and repeated during follow-up, more frequently in high-risk patients [6, 532]. The bladder diary can aid in detecting MS patients that require urodynamic investigations [534]. In addition, bladder wall thickness can be measured on ultrasonography as an additional risk assessment for upper tract damage [535], although a 'safe' cut-off threshold for this has not been agreed [536]. The utility of DMSA (dimercaptosuccinic acid) for follow-up of neuro-urological patients has not been fully evaluated [537]. Any significant clinical change warrants further, specialised, investigation [6, 532]. However, there is a lack of high level evidence studies on this topic and every recommendation must be viewed critically in each individual neuro-urological patient [132].

The increased prevalence of muscle invasive bladder cancer in neuro-urological patients also warrants long-term follow-up [260]. The exact frequency of cystoscopy with or without cytology remains unknown, but presence of risk factors similar to the general population should trigger further investigation [538].

Adolescent patients with neurological pathology are at risk of being lost to follow-up during the transition to adulthood. It is important that a standardised approach during this transition is adopted to improve follow-up and specific treatment during adult life [539].

3.7.2 Summary of evidence and recommendations for follow-up

Summary of evidence	LE
Neuro-urological disorders are often unstable, and the symptoms may vary considerably; therefore, regular follow-up is necessary.	4

Recommendations	Strength rating
Assess the upper urinary tract at regular intervals in high-risk patients.	Strong
Any significant clinical changes should instigate further, specialised, investigation.	Strong
Perform urodynamic investigation as a mandatory baseline diagnostic intervention in high-risk patients at regular intervals.	Strong

3.8 Conclusions

Neuro-urological disorders have a multifaceted pathology. They require an extensive and specific diagnosis before one can embark on an individualised therapy, which takes into account the medical and physical condition of the patient and the patient's expectations about their future. The urologist can select from a wealth of therapeutic options, each with its own pros and cons. Notwithstanding the success of any therapy embarked upon, close surveillance is necessary for the patient's entire life.

These Guidelines offer you expert advice on how to define the patient's neuro-urological symptoms as precisely as possible and how to select, together with the patient, the appropriate therapy. This last choice, as always, is governed by the golden rule: as effective as needed, as non-invasive as possible.

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5. CONFLICT OF INTEREST

All members of the Neuro-urology 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. 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 and travel and meeting expenses. No honoraria or other reimbursements have been provided.

6. CITATION INFORMATION

The format in which to cite the EAU Guidelines will vary depending on the style guide of the journal in which the citation appears. Accordingly, the number of authors or whether, for instance, to include the publisher, location, or an ISBN number may vary.

The compilation of the complete Guidelines should be referenced as:
EAU Guidelines. Edn. presented at the EAU Annual Congress Paris 2024. ISBN 978-94-92671-23-3.

If a publisher and/or location is required, include:
EAU Guidelines Office, Arnhem, The Netherlands. http://uroweb.org/guidelines/compilations-of-all-guidelines/

References to individual guidelines should be structured in the following way:
Contributors' names. Title of resource. Publication type. ISBN. Publisher and publisher location, year.

EAU Guidelines on

Sexual and Reproductive Health

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European Association of Urology

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1. INTRODUCTION

1.1 Aims and Objectives

The European Association of Urology (EAU) Sexual and Reproductive Health Guidelines aim to provide a comprehensive overview of the medical aspects relating to sexual and reproductive health in adult men. These Guidelines cover the former EAU Guidelines on Male Sexual Dysfunction, Male Infertility and Male Hypogonadism.

It must be emphasised that 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 - while taking personal values and preferences/individual circumstances of patients into account. Guidelines are not mandates and do not purport to be a legal standard of care.

1.2 Panel Composition

The EAU Sexual and Reproductive Health Guidelines Panel consists of an international multi-disciplinary group of urologists, endocrinologists and a psychologist. 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/sexual-and-reproductive-health/.

1.3 Available Publications

A quick reference document, the Pocket Guidelines, is available. This is an abridged versions that may require consultation together with the full-text version. A number of scientific publications are also available. All documents can be viewed through the EAU website: http://www.uroweb.org/guideline/sexual-and-reproductive-health/.

1.4 Publication History

The EAU Sexual and Reproductive Health Guidelines were first published in 2020. This 2024 document presents a limited update of the 2023 publication.

1.5 Changes in the Guideline for 2024

The 2024 Sexual and Reproductive Health Guidelines have undergone a major revision and restructuring of the full text as well as a review of all recommendations.

2. METHODOLOGY

2.1 Methods

Recommendation within the Guidelines are developed by the panels to prioritise clinically important care decisions. The strength of each recommendation is determined by the balance between desirable and undesirable consequences of alternative management strategies, the quality of the evidence (including certainty of estimates), and the nature and variability of patient values and preferences. This decision process, which can be reviewed in the strength rating forms which accompany each guideline statement, addresses a number of key elements:

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

Strong recommendations typically indicate a high degree of evidence quality and / or a favourable balance of benefit to harm and patient preference. Weak recommendations typically indicate availability of lower quality evidence, and/or equivocal balance between benefit and harm, and uncertainty or variability of patient preference [2].

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 this address.

2.2 Review

The EAU Sexual and Reproductive Health Guidelines were peer-reviewed prior to publication in 2020. The new priapism section was reviewed prior to publication in 2021. In 2023 the newly added section on penile size abnormalities and dysmorphophobia was reviewed prior to publication. The Panel would like to acknowledge the contribution of Dr. Miguel Ricou from the Department of Community Medicine, Information and Health Decision Sciences at the Faculty of Medicine, University of Porto, Portugal, for his expertise and time in reviewing the penile size abnormalities and dysmorphophobia section from a bioethics perspective.

3. MALE HYPOGONADISM

3.1 Definition, epidemiology and classification of male hypogonadism

3.1.1 ***Definition***

Male hypogonadism is a clinical syndrome which comprises of symptoms with or without signs and biochemical evidence of testosterone deficiency. Hypogonadism is associated with decreased testicular function and production of androgens and/or impaired sperm production [3]. This may be caused by impaired testicular function (hypergonadotropic hypogonadism or primary hypogonadism) or as a result of inadequate stimulation of the testes by the hypothalamic-pituitary axis (hypogonadotropic hypogonadism or secondary hypogonadism) (Table 1) or uncommonly by reduced ability of testosterone to stimulate the androgen receptor at the cellular level. Hypogonadism can adversely affect multiple organ functions and quality of life (QoL) [3, 4]. This chapter specifically addresses the management of adult male hypogonadism also called late-onset hypogonadism (LOH). Some insights related to congenital or pre-pubertal hypogonadism are also provided.

3.1.2 ***Epidemiology***

The prevalence of LOH increases with age, with the major causes being obesity, other comorbidities (e.g., diabetes) and overall poor health [5]. The incidence of hypogonadism has been reported to be between 12.3 and 11.7 cases per 1,000 people per year [6, 7]. Aging accounts for a low percentage of hypogonadism, as there is only a small gradual decline in testosterone, up to the age of 80 years, in healthy ageing men [5]. In men aged 40-79 years, the incidence of symptomatic hypogonadism varies between 2.1 and 5.7% [6, 8, 9].

There is a high prevalence of LOH within specific populations, including patients with obesity, type 2 diabetes (T2DM), metabolic syndrome (MetS), cardiovascular diseases (CVD), chronic obstructive pulmonary disease (COPD), renal disease and cancer [9]. In particular low testosterone levels are relatively common in men with T2DM [10, 11] and in those with metabolic derangements.

Klinefelter syndrome, a trisomy associated with a 47, XXY karyotype, is the most prevalent genetic cause of primary hypogonadism, with a global prevalence of 1/500-1,000 live male births [12-15]. However, < 50% of individuals with Klinefelter syndrome are diagnosed during their lifetime [16].

3.1.3 ***Classification***

Male hypogonadism can be classified according to the aetiology into primary hypogonadism or secondary hypogonadism (Table 1) [3, 17]. A compensated or subclinical form of hypogonadism, characterised by normal testosterone serum levels and elevated luteinising hormone (LH) production, has also been reported [18]; the clinical significance of this condition is unclear [18-21].

The classification of hypogonadism has also been divided into two broad categories: 'Classical/Organic' and 'Functional, often but not correctly identified as LOH [58]. The clinical effects of testosterone deficiency are however common to all patients independent of the cause of the hypogonadism; although, they may vary in severity or as a result of age of onset (see below). Classical hypogonadism includes: congenital or acquired diseases causing structural and/or irreversible impairment of the pituitary and/or testes. Functional hypogonadism is diagnosed on the absence of any recognised organic alterations in the HPG axis and it is mainly a consequence of comorbidities, affecting the Hypothalamic-Pituitary-Testicular (HPT) axis and should be treated first by resolving or improving any underlying conditions (e.g., anorexia in younger male subjects). Late onset hypogonadism, conversely represents even a broader clinical entity including adulthood onset forms which can have either organic or functional origin and can be primary or secondary [22] (see below). Late onset hypogonadism is frequently diagnosed in the absence of an identifiable classical cause of hypogonadism, which becomes more prevalent with age, usually occurring, but not exclusively, in men aged > 40 years. By definition LOH must comprise both persistent specific symptoms and biochemical evidence of testosterone deficiency [3, 23].

Finally, hypogonadism can also result from several conditions leading to reduced sensitivity/insensitivity to testosterone and its metabolites [3].

The current guidelines maintain a classification of Primary and Secondary Hypogonadism, with special reference to LOH.

The classification, based on the aetiology of hypogonadism, allows clinicians to adequately select appropriate treatment. In patients with secondary hypogonadism, both fertility and testosterone normalisation can be theoretically achieved with adequate treatment, whereas in primary hypogonadism only testosterone therapy can be considered [3, 17] (Table 1). However, it should also be recognised that symptoms and signs of hypogonadism can be similarly independent of the site of origin of the disease. Conversely, the age of onset of hypogonadism can influence the clinical phenotype [24]. Accordingly, early onset, such as that occurring during foetal life, the clinical phenotype can span from an almost complete female phenotype (e.g., complete androgen insensitivity or enzymatic defects blocking androgen synthesis) to various defects in virilisation. In the case of a pre- or peri-pubertal appearance of hypogonadism due to a milder central (isolated hypogonadotropic hypogonadism [IHH]) or a peripheral defect (such as in Klinefelter syndrome), there may be delayed puberty with an overall eunuchoid phenotype. Finally, when hypogonadism arises post-puberty, particularly with advancing age, symptoms may manifest subtly and frequently overlap with the natural ageing process, leading to confusion [24].

Table 1: Classification of male hypogonadism

PRIMARY HYPOGONADISM (hypergonadotropic hypogonadism)	
Congenital or developmental disorders	
Common causes	*Uncommon causes*
• Klinefelter syndrome	• Rare chromosomal abnormalities - (XX male, 47 XYY and 48 XXYY syndrome • 21 Trisomy (Down syndrome) • Noonan syndrome • Autosomal translocations1 • Defects of testosterone biosynthesis • CAH (testicular adrenal rest tumours) • Disorders of sex development (gonadal • dysgenesis) • LHR gene mutations • Myotonic dystrophy (including type I and II) • Uncorrected cryptorchidism (including INSL3 • and LGR8 mutations) • Bilateral congenital anorchia • Sickle cell disease • Adreno-leukodystrophy
Acquired disorders	
Drug-induced	*Localised problems*
• Chemotherapy agents • Alkylating agents • Methotrexate • Testosterone synthesis inhibitors - Ketoconazole, Aminoglutethimide, Mitotane and Metyrapon	• Bilateral surgical castration or trauma • Testicular irradiation • Orchitis (including mumps orchitis) • Autoimmune testicular failure • Testicular Torsion • Alcohol/Cirrhosis • Environmental Toxins
Systemic diseases/conditions with hypothalamus/pituitary impact	
• Chronic systemic diseases* • Chronic organ failure* • Glucocorticoid excess (Cushing syndrome)* • Ageing* • HIV	• Malignancies – Lymphoma and Testis cancer • Spinal cord injury • Vasculitis • Infiltrative diseases (amyloidosis; leukaemia)

SECONDARY HYPOGONADISM (hypogonadotropic hypogonadism)	
Congenital or developmental disorders	
Common causes	*Uncommon causes*
• Haemochromatosis*	• Combined hormone pituitary deficiency • Idiopathic hypogonadotropic hypogonadism • IHH with variants: Normosmic IHH, Kallmann syndrome, isolated LH β gene mutations and Prader-Willi syndrome
Acquired disorders	
Drug-induced	*Localised problems*
• Oestrogens • Testosterone or androgenic anabolic steroids • Progestogens (including cyproterone acetate) • Hyperprolactinemia-induced drugs • Opiates - GnRH agonist or antagonist and glucocorticoids	• Traumatic brain injury • Pituitary neoplasm (micro/macro-adenomas) • Hypothalamus tumours • Pituitary stalk diseases • Iatrogenic - surgical hypophysectomy and pituitary or cranial irradiation • Inflammatory and infectious diseases -lymphocytic hypophysitis; pituitary infections; granulomatous lesions; sarcoidosis; Wegener's granulomatosis; other granulomatosis and encephalitis • Langerhans' histiocytosis • Hyperprolactinaemia, as a consequence of localised problems (hypothalamus-pituitary mass)
Systemic diseases/conditions impacting the hypothalamus/pituitary	
• Chronic systemic diseases* - Type 2 diabetes mellitus/Metabolic Syndrome/metabolic diseases; HIV infection; chronic organ failure; and chronic Inflammatory Arthritis • Glucocorticoid excess (Cushing syndrome)* • Eating disorders* • Endurance exercise • Acute and critical illness • Ageing*	• Spinal cord injury • Transfusion-related iron overload (β-thalassemia)
ANDROGEN RESISTANCE/DECREASED TESTOSTERONE BIOACTIVITY	
Congenital or developmental disorders	
• Aromatase deficiency • Kennedy diseases (spinal and bulbar muscular atrophy) and other extensions of CAG repeats • Partial or complete androgen insensitivity • 5α reductase type II (5aR) deficiency	
Acquired disorders	
Drug-induced	*Localised problems*
• Drug-induced AR blockage - steroidal antiandrogen, cyproterone acetate and spironolactone • Non-steroidal antiandrogen – flutamide, bicalutamide and nilutamide • Drug-induced 5α reductase (5aR) activity blockade – finasteride and dutasteride • Drug-induced ER blockade – clomiphene, tamoxifen and raloxifene • Drug-induced aromatase activity blockade – letrozole, anastrozole and exemestane • Increased Sex Hormone Binding Globulin (SHBG)	• Coeliac disease

** Conditions acting at central and peripheral levels resulting in either primary and secondary hypogonadism.*

[1] Different autosomal translocations can cause rare cases of hypogonadism and infertility.

A brief discussion on the physiology of testosterone production can be found in Appendix 1, online supplementary evidence.

3.2 Comorbidities associated with male hypogonadism

3.2.1 ***Obesity***

Low testosterone levels are common in men with obesity. Male hypogonadism is associated with a greater percentage of fat mass and a lower lean mass compared to men with adequate testosterone levels [25, 26]. Low levels of testosterone are strongly linked to heightened visceral adiposity. Additionally, they result in lipid accumulation in the liver and muscle, correlating with atherosclerosis [25, 26].

3.2.2 ***Metabolic Syndrome/Type 2 Diabetes***

Hypogonadism is frequently associated with MetS or its related components, including central obesity, hyperglycaemia, insulin resistance and dyslipidaemia and arterial hypertension [27].

Several randomised controlled trials (RCTs) have demonstrated that testosterone therapy may improve insulin resistance and hyperglycaemia and lower total and low-density protein
(LDL) cholesterol [28-33]. Testosterone therapy in hypogonadal T2DM improved glycaemic control in some RCTs and registry trials; however, there is no conclusive evidence [29, 34, 35]. A large placebo-controlled RCT, including 1,007 patients with impaired glucose tolerance or newly-diagnosed T2DM and total testosterone < 14 nmol/L showed that testosterone therapy for two years reduced the proportion of patients with T2DM regardless of a lifestyle programme [33]. Similarly, a registry study reported that testosterone therapy was associated in time with remission of T2DM [34]. High-density lipoprotein (HDL)-cholesterol may decrease, remain unchanged or increase with testosterone therapy.

Testosterone therapy in men with MetS and low testosterone has been shown to reduce mortality compared to untreated men [36, 37], although no conclusive evidence is available.

Erectile dysfunction (ED) is common in men with MetS and T2DM (up to 70% of patients). The causes of ED are multi-factorial and 30% of men with ED have co-existing testosterone-deficiency/hypogonadism. Some evidence has suggested that ED is only found in men with T2DM and clearly reduced testosterone levels (< 8 nmol/L or 2.31 ng/mL) [38]. From a pathophysiological perspective, it has been reported that this is because ED is predominantly caused by vascular and neuropathic disease, and therefore not likely in men who do not have established vascular disease. Therefore, men presenting with ED should be screened for MetS. Likewise, patients with ED and diabetes may be offered testosterone measurement.

Placebo-controlled RCTs of testosterone therapy in T2DM have demonstrated improved sexual desire and satisfaction, although data on erectile function were limited [29, 38]. Similar results were derived from a meta-analysis of published trials [39]. Accordingly, a large two-year RCT of testosterone undecanoate vs. placebo showed that testosterone therapy significantly improved sexual function and ED in men with impaired glucose tolerance or newly-diagnosed T2DM low testosterone (< 14 nmol/L) [33].

Testosterone therapy has been associated with a reduced percentage of body fat and increase in lean body mass [40]. Data from a registry study have suggested that testosterone therapy with long-acting intramuscular testosterone undecanoate over eleven years was associated with a substantial but gradual loss of weight, along with a reduction in waist circumference [41]

3.2.3 ***Sars-CoV-2 / COVID-19***

Data seem to suggest that low circulating testosterone levels are more frequently associated with worse clinical outcomes in men with COVID-19 [42-49]. Accordingly, a cohort study, analysing two large academic health systems databases, including 723 men with a history of COVID-19 reported that hypogonadal men had a higher risk of being hospitalised [50]. In addition, a meta-analysis suggested that reduced testosterone levels detected at hospital admission for COVID-19 are associated with a four- five-fold increased risk of being admitted to the Intensive Care Unit (ICU) or dying, after adjustment for potential confounders [51].

Although no information on the role of testosterone therapy in the acute phase of the disease is available currently, data also showed that the hypogonadal patients under testosterone therapy had a reduced risk to be hospitalised after SARS-CoV-2 infection [50]. However, whether or not low testosterone can directly contribute to worse COVID-19 outcomes is still under investigation. The possibility that low testosterone in the acute phase of COVID-19 infection represents an adaptive response mechanism to dampen non-essential activities non

conducive to recovery (physical and sexual activities) by turning off testosterone-dependent functions, cannot be excluded [52, 53]. Accordingly, a meta-analysis showed that secondary or mixed hypogonadism is more frequently observed in the acute phase of the infection [51].

Studies evaluating patients in the recovery phase of COVID-19 have documented either restored [54, 55] or persistently low testosterone levels in the majority of cases [56]. A longitudinal evaluation study showed that during the recovery phase a further improvement of testosterone levels can be observed up to twelve months after COVID-19. Male subjects who have recovered from COVID-19 should be accurately followed-up to exclude any long-term andrological consequences including impairment in sperm and testosterone production [51].

Table 2: Main factors associated with an increase or reduction of SHBG circulating levels

SHBG increase	SHBG decrease
• Drugs: anticonvulsants, oestrogens, thyroid hormone • Hyperthyroidism • Hepatic disease • Ageing • Smoking • AIDS/HIV	• Drugs: growth hormone (GH), glucocorticoids, testosterone, anabolic androgenic steroids • Hypothyroidism • Obesity • Acromegaly • Cushing's disease • Insulin resistance (MetS/T2DM) • Non-alcoholic fatty liver disease (NAFLD), • Nephrotic syndrome

3.3 Late-onset hypogonadism

Testosterone production declines with ageing. The European Male Aging Study (EMAS) reported a 0.4% per annum (log hormone-age) decrease in total testosterone and a 1.3% per annum decline in free testosterone (fT) [5]. Late onset hypogonadism is the term frequently used to describe this phenomenon and the detection of hypogonadism in adulthood. Evidence indicates that several associated diseases and chronic comorbidities can interfere with the HPG axis leading to the development of primary hypogonadism or, more frequently, secondary hypogonadism in adulthood, thus significantly influencing the physiological age-dependent decline of testosterone. Combining the data from three different waves of the Massachusetts Male Aging Study (MMAS), demonstrated that associated comorbidity and obesity significantly decreased, whereas smoking tended to increase total, free and bio-available testosterone concentrations [57]. Data derived from the EMAS confirmed these findings [5, 19]. Based upon these data and other evidence, as previously reported the concept of *functional and organic hypogonadism* has been more recently introduced (see above) [58]. Considering that suppression of HPG axis activity is functional, and potentially reversible by empiric measures, such as weight loss, the need for testosterone therapy has been questioned [58].

3.3.1 Clinical Diagnosis and Evaluation

The mainstay of LOH diagnosis includes signs and symptoms consistent with hypogonadism, coupled with biochemical evidence of low morning serum total testosterone levels on two or more occasions, measured with a reliable assay and in fasting conditions.

3.3.2 History taking

Specific symptoms associated with hypogonadism, including LOH, are shown in Table 3. These symptoms are non-specific and need to be recorded and taken in context with the clinical and biochemical state. Several self-reported questionnaires or structural interviews have been developed for screening of hypogonadism. Although these case-history tools have demonstrated clinical utility in supporting the biochemical diagnosis of hypogonadism, or in the assessment of testosterone therapy outcomes, their specificity remains poor and they should not be used for a systematic screening of hypogonadal men [59]. Headache and/or visual disturbance may indicate a pituitary-related disorder. History of surgical intervention for cryptorchidism or hypospadias must be taken into account as possible signs of congenital defects. Chronic and systemic comorbidities must be comprehensively investigated in every patient. Use of drugs that potentially interfere with the HPG axis should be excluded (Table 1). Acute diseases are associated with development of functional hypogonadism and determination of serum total testosterone levels should be avoided in these conditions; however, the role of testosterone in the case of acute illness remains to be clarified [42, 46, 51, 60]. Fertility issues should be always discussed.

Table 3: Specific symptoms associated with LOH

	Sexual symptoms	Physical symptoms	Psychological symptoms
More specific	• Reduced libido • Erectile dysfunction • Decreased spontaneous/morning erections	• Decreased vigorous activity • Difficulty walking > 1 km • Decreased bending	• Low mood/mood deflection • Decreased motivation • Fatigue
Less specific	• Reduced frequency of sexual intercourse • Reduced frequency of masturbation • Delayed ejaculation	• Hot flushes • Decreased energy • Decreased physical strength/function/ activity	• Concentration difficulties • Sleep disturbances

3.3.3 ***Physical examination***

Since obesity is frequently associated with hypogonadism (mostly functional), the determination of body mass index (BMI) and the measurement of waist circumference are strongly recommended in all individuals. Testicular and penile size, as well as the presence of sexual secondary characteristics can provide useful information regarding overall androgen status. In addition, upper segment/lower segment ratio (n.v. > 0.92) and arm-span to height ratio (n.v. < 1.0) can be useful to identify a eunuchoid body shape, especially in subjects with pre-pubertal hypogonadism or delayed puberty. Finally, digital rectal examination (DRE) should be performed in all subjects to exclude prostate abnormalities before testosterone therapy (any type) or to support suspicion of hypogonadism (in case of reduced volume) [61].

3.3.4 ***Laboratory Diagnostics***

Testosterone levels are produced in a circadian variation, which may persist in ageing men [62, 63]. Testosterone levels are also potentially influenced by food intake [64]; therefore, serum total testosterone should be measured in fasting conditions in the morning (between 07.00 and 11.00 hours). A confirmatory measurement should always be undertaken in the case of a primary pathological value, and before starting any testosterone therapy.

Liquid Chromatography-Tandem Mass Spectrometry (LC-MS/MS) represents the most accurate method for sex steroid evaluation; however, standardised automated platform immuno-assays for total testosterone assessment demonstrate a good correlation with LC-MS/MS [65]. Available immuno-assays are not able to provide an accurate estimation of fT; therefore, direct fT evaluation with these methods is not recommended and should be avoided [66]. Equilibrium dialysis is the most accurate method for total testosterone measurement and FT calculation [67]. Alternatively, fT can be derived from specific mathematical calculations using total testosterone as derived by common immunoassays and taking into account serum sex hormone binding globulin (SHBG) and albumin levels [68] (http://www.issam.ch/freetesto.htm).

Data from meta-analyses have shown that testosterone therapy is ineffective when baseline levels are > 12 nmol/L (3.5 ng/mL). Positive outcomes are documented when testosterone levels are < 12 nmol/L, being higher in symptomatic patients with more severe forms of hypogonadism (< 8 nmol/L). Hence, 12 nmol/L should be considered as a possible threshold for starting testosterone therapy in the presence of hypogonadal symptoms [40, 69].

In clinical conditions that may interfere with SHBG levels, evaluation of fT should be considered to better estimate actual androgen levels (Figure 1). Unfortunately, despite its potential clinical value [70], no validated thresholds for fT are available from clinical studies and this represents an area of uncertainty; however, data from the EMAS indicated that fT levels < 220 pmol/L (6.4 ng/dL) increased the likelihood to correct identify hypogonadism as compared with total testosterone level alone, particularly when total testosterone levels are between 8.0 and 11 nmol per litre [8, 71, 72].

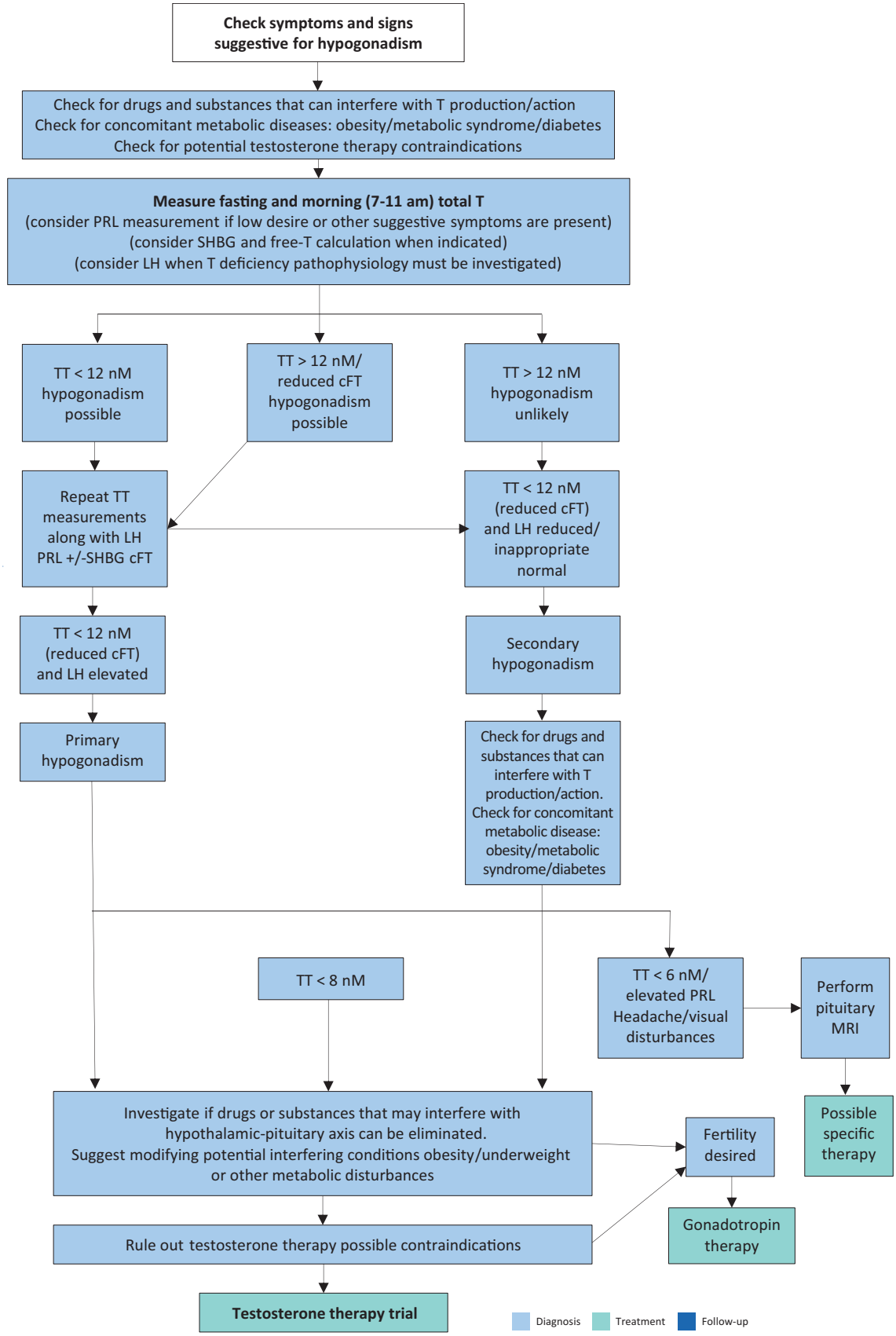
The determination of LH must be performed along with prolactin (PRL) when pathological total testosterone levels are detected, in order to correctly define the underlying conditions and exclude possible organic causes (Figure 1). Follicle-stimulating hormone determination can further support the diagnosis of primary or secondary hypogonadism [21, 73]. Due to its negative influence on libido, PRL can also be considered as first-line screening in patients with reduced sexual desire. In addition, contrast-enhanced pituitary magnetic resonance imaging (MRI) scanning, as well as other pituitary hormone evaluations, is required in the presence of specific symptoms such as visual disturbances, headache and when hyperprolactinemia is confirmed [74, 75]. Limited evidence suggests also performing pituitary MRI in the case of severe hypogonadism (< 6 nmol/L, 1.75 ng/mL) with inadequate gonadotropin levels (Figure 1) [74-76].

3.3.5 *Summary of evidence and recommendations for the diagnostic evaluation and screening of LOH*

Summary of evidence	LE
Sexual symptoms are the most specific symptoms associated with late-onset hypogonadism (LOH).	1a
Diagnosis of LOH should be based on specific signs and symptoms of androgen deficiency, together with consistently low serum testosterone levels.	1a
Total testosterone 12 nmol/L (3.5 ng/mL) represents a reliable threshold to diagnose LOH.	1a
Functional hypogonadism is a consequence of comorbidity/concomitant drugs, which can impair testosterone production in adulthood. The diagnosis of functional hypogonadism is a diagnosis of exclusion, after ruling out organic causes of hypogonadism.	4
Calculated free-testosterone of < 220 pmol/L has been suggested as a possible cut-off to diagnose LOH.	3
Self-reported questionnaires and structural interviews have been developed for screening of hypogonadism but their specificity remains poor.	2a

Recommendations	Strength rating
Diagnostic evaluation	
Check for concomitant diseases, drugs and substances that can interfere with testosterone production/action.	Strong
Measure total testosterone in the morning (between 07.00 and 11.00 hours) and in the fasting state, with a reliable laboratory assay.	Strong
Repeat total testosterone on at least two separate occasions when < 12 nmol/L and before starting testosterone therapy.	Strong
Use 12 nmol/L total testosterone (3.5 ng/mL) as a reliable threshold to diagnose late onset hypogonadism (LOH).	Strong
Measure sex hormone-binding globulin and free-testosterone calculation when indicated	Strong
Analyse luteinising hormone and follicle-stimulating hormone serum levels to differentiate between the different types of hypogonadism.	Strong
Measure prolactin (PRL) levels if evidence of low sexual desire (or other suggestive signs/symptoms) and secondary hypogonadism is present.	Strong
Perform pituitary magnetic resonance imaging (MRI) in secondary hypogonadism, with elevated PRL or symptoms specific of a pituitary mass and/or presence of other anterior pituitary hormone deficiency.	Strong
Perform pituitary MRI in secondary severe hypogonadism (total testosterone < 6 nmol/L).	Weak
Screening	
Screen for late onset hypogonadism (LOH) only in symptomatic men.	Strong
Do not use structured interviews and self-reported questionnaires for systematic screening for LOH as they have a low specificity.	Strong

Figure 1: Diagnostic evaluation of Late-Onset Hypogonadism



TT = total testosterone; cFT = calculated free testosterone; PRL = prolactin; SHBG = sex hormone-binding globulin; LH = luteinising hormone; MRI = Magnetic resonance imaging.

3.4 Treatment of Classical and LOH

3.4.1 Indications and contraindications for treatment of hypogonadism

Patients with symptomatic hypogonadism (total testosterone < 12 nmol/L) without specific contraindications are suitable candidates to receive testosterone therapy (Table 4).

Absolute contraindications are untreated breast and prostate cancer (PCa). Similarly, conditions such as cardiovascular events as well as uncontrolled or poorly controlled congestive heart failure should be considered when prescribing testosterone therapy [77]. Conversely, severe lower urinary tract symptoms (LUTS) [International Prostate Symptom Score (IPSS) score > 19] represent a relative contraindication, as there is insufficient data on the long-term effects of testosterone therapy in these patients [66]. A positive family history for venous thromboembolism requires further analysis to exclude a condition of undiagnosed thrombophilia-hypofibrinolysis [78]. These patients need to be carefully counselled prior to testosterone therapy initiation. A haematocrit (HCT) > 54% should require testosterone therapy withdrawal, reduction in dose, change of formulation and venesection depending on the clinical situation to avoid any potential cardiovascular complications. Lower baseline HTC (48-50%) should be carefully evaluated before testosterone therapy initiation, to avoid pathological increases during treatment, especially in high-risk men such as those with COPD or Obstructive Sleep Apnoea Syndrome (OSAS). Accordingly, the Framingham Heart Study showed that HCT > 48% represented a condition associated with increased risk of coronary artery disease (CAD) and mortality and was associated with cardiovascular disorders [79]. Testosterone therapy suppresses gonadotropin and endogenous testosterone secretion as well as spermatogenesis [80]; therefore, testosterone therapy is contraindicated in individuals who desire fertility [81]. Secondary hypogonadism is characterised by low or inappropriately normal gonadotropin levels; therefore, the rationale is to substitute the gonadotropin deficiency with simultaneously FSH and LH analogues, if fertility is desired [82].

Table 4: Main contraindications of testosterone therapy

Absolute contraindications	Locally advanced or metastatic prostate cancer (PCa) Male breast cancer Men with an active desire to have children Haematocrit ≥ 54% Uncontrolled or poorly controlled congestive heart failure
Relative contraindication	IPSS score > 19 Baseline haematocrit 48-50% Familial history of venous thromboembolism

3.4.2 Testosterone therapy outcomes

3.4.2.1 Sexual dysfunction

Sexual concerns are the main symptoms of hypogonadal patients [3, 8, 83, 84]. A consistent body of evidence shows that testosterone therapy in hypogonadal men (total testosterone < 12 nmol/L) may have a beneficial effect on several aspects of sexual life; in contrast, there is no evidence of benefits in using testosterone therapy for treating sexual dysfunction in eugonadal men [69, 85-87]. The beneficial effect on sexual function seems to be more related to testosterone level normalisation than the specific testosterone formulations used [87, 88].

A meta-analysis of placebo-controlled RCTs showed that testosterone therapy significantly improves erectile function (as measured by IIEF-Erectile Function domain score) and that patients with more severe hypogonadism (i.e., total testosterone < 8 nmol/L) are more likely to achieve better improvement than patients with milder hypogonadism (i.e., total testosterone < 12 nmol/L) [69]. Similar results were observed for sexual desire; however, the presence of metabolic comorbidity (such as diabetes and obesity) decreased the magnitude of these improvements. In particular, testosterone therapy alone resulted in a clinically effective outcome only in patients with milder ED [69]. Similar results have also been confirmed in an update analysis [89] and in a recently published Cochrane review [1970]. In line with these data, report from the non-inferiority "Testosterone Replacement Therapy for Assessment of Long-term Vascular Events and Efficacy Response in Hypogonadal Men (TRAVERSE)" study, showed in middle-aged and older hypogonadal (total testosterone < 10.4 nmol/L) men with pre-existing or a high risk of CVD, testosterone therapy with gel for two years improved sexual activity, hypogonadal symptoms, and sexual desire, but not erectile function [90].

Other sexual function parameters, such as intercourse, orgasm and overall satisfaction, were all improved compared with placebo [69, 89]. Men with a comorbidity, such as T2DM, usually show modest improvements in terms of sexual function after testosterone therapy and may potentially require concomitant phosphodiesterase type 5 inhibitors (PDE5Is) to improve effectiveness [3, 87]. A meta-analysis including 913 patients derived from eight RCTs suggested that combination therapy (testosterone and PDE5Is) was superior when compared

to PDE5Is alone in improving erectile function [92]. The specific beneficial effect derived from the combined use of testosterone therapy and PDE5Is is unclear [85]. Similarly, information related to the combined use of testosterone therapy with other ED drug therapies is lacking [3, 87].

The Sexual Function Trial of the Testosterone Trials (TTrials) (one of the largest placebo-controlled trials on testosterone therapy) documented consistent improvements in 10 of 12 measures of sexual activities in older (≥ 65 years) hypogonadal men, particularly in frequency of intercourse, masturbation and nocturnal erections (as measured by PDQ-Q4) [93, 1973]. The magnitude in improvement was shown to be proportional to the increase in serum total testosterone, fT and E2 levels, it was not possible to demonstrate a threshold level [94]. A study of 220 men with MetS with or without T2DM also found that sexual function improved in men who reported sexual problems with improvement in IIEF scores, with specific increases in libido and sexual satisfaction [29].

3.4.2.2 Vitality and physical strength

The role of testosterone in stimulating muscle growth and strength is well established. Accordingly, androgenic-anabolic steroids (AAS) have been used as performance-enhancing agents to increase physical performance in competitive sport [95]. In this regard, testosterone therapy in hypogonadal men has been shown to increase muscle mass and reduce fat mass, with limited effects on final weight [40]. Despite this evidence, the role of testosterone therapy in older men with mobility limitations remains unclear. The National Health and Nutrition Examination Survey 1999-2004 [96] was unable to detect any association between overall circulating testosterone levels and the amount of physical activity. However, among non-obese men, those in the highest physical activity tertile were significantly less likely to have low or low-normal testosterone than those in the lowest tertile. Data from TTrials indicated that testosterone therapy did not substantially increase the fraction of men whose six-minute walking distance increased > 50 m or the absolute increase in the distance walked by those enrolled in the physical function trial [93]. However, when the whole population of the TTrials was considered, a significant, although modest, positive effect on these two parameters was reported [93]. Similar data were derived from the Vitality Trial [93]. As support of the aforementioned considerations, a recent meta-analysis including 2043 subjects older than 60 years failed to show a significant improvement of muscle strength of testosterone therapy when compared to placebo [97].

3.4.2.3 Mood and cognition

Several observational studies have documented a relationship between depressive symptoms, reduced QoL and hypogonadism [98, 99]. However, the specific relationship between hypogonadism and the incidence of depression is still unclear [99]. Only a few placebo-controlled RCTs have investigated the role of testosterone therapy in improving depressive symptoms. Data derived from TTrials showed that testosterone therapy improved mood, and depressive symptoms as continuous measures using several instruments [93]. However, the final effect was small in magnitude. In line with this data, the largest meta-analysis of available studies, including 1,890 hypogonadal men (baseline total testosterone < 12 nmol/L or fT < 225 pmol/L) men from 27 RCTs, documented that the positive effect of testosterone therapy was particularly evident in patients with milder symptoms [100]. The BLAST study of testosterone therapy in T2DM reported that those men with depression were less likely to respond with regards to symptoms of sexual dysfunction compared to men without depression [35].

Robust data on the effect of testosterone therapy on QoL are limited. Although recent meta-analyses suggest a significant effect of testosterone therapy over placebo, the magnitude is low and the heterogeneity high, therefore reducing the scientific value of the effect [88, 101].

The role of testosterone therapy in patients with cognitive impairment is even more uncertain. The TTrials evaluated the effect of testosterone therapy in 493 individuals with age-associated memory impairment to assess possible improvement of several aspects of cognitive function. However, results failed to demonstrate any beneficial effect of testosterone therapy in improving cognitive function [93]. Similarly, a meta-analysis involving 17 studies enrolling 1,438 patients with a mean age of 70.4 years and a mean follow-up of 45.6 weeks did not find any effect of testosterone therapy on cognitive domains [102].

3.4.2.4 Body composition and metabolic profile

Late onset hypogonadism is associated with a greater percentage of fat mass and a lesser lean mass compared to testosterone-repleted men [103]. The major effect of low testosterone is to increase visceral adiposity but it also leads to deposition of lipids in the liver and muscle and is associated with atherosclerosis [25]. Some published data have suggested that testosterone therapy reduces percentage body fat and increases lean mass [104]. Testosterone therapy has also been found to decrease waist circumference, body weight and BMI, with these effects more predominant after twelve months of treatment [104-106]. Over two years, the T4DM RCT reported that men on testosterone therapy and a lifestyle programme had a greater reduction in waist circumference, total and abdominal fat mass and an increase in total and arm muscle mass and an increased

strength in the non-dominant hand compared to a lifestyle programme alone [33]. There was a trend toward reduction in body weight although this approached significance but did not reach significance. The latter result is probably compounded by the increase in muscle mass as well as the decrease in fat mass. However, it should be recognised that the results of previous studies are mainly derived from registry and observational trials, which have important limitations due to the risk of selection bias for the non-random assignment of testosterone exposure. Accordingly, data derived from RCTs showed only an improvement of fat mass and lean mass of the same amount without any modifications in body weight [40]. A meta-analysis including seventeen RCTs specifically investigated the role of testosterone therapy on several metabolic parameters in patients with T2DM and/or MetS [39]. In line with what was reported in the general population, testosterone therapy was associated with an improvement in body composition either in T2DM or MetS without any effects on body weight. Similarly positive effects were also observed on fasting glycemia and insulin resistance (HOMA index) whilst more conflicting data were obtained for HbA1c and lipid profile [39].

3.4.2.5 Bone

Evidence suggests that bone mineralisation requires circulating sex steroids within the normal range [107]. The possible association between mild hypogonadism and osteopenia/osteoporosis is weak, whereas severe hypogonadism (total testosterone < 3.5 nM) is frequently associated with bone loss and osteoporosis, independent of patient age [107]. Three independent meta-analyses showed a positive effect of testosterone therapy on bone mineral density (BMD), with the highest effect at the lumber level [108-110]. Interestingly, the latter meta-analysis has provided novel evidence that the role of testosterone on BMD was even higher in patients with diabetes [110], who are at a higher risk of hypogonadism and bone fracture [39, 111, 112]. Similarly, data derived from TTrials and the T4DM studies confirmed that testosterone therapy increased BMD in hypogonadal ageing men [93, 113]. However, available data are insufficient to determine the effect of testosterone therapy alone on the risk of fractures [107]. Recent data from the aforementioned TRAVERSE trial quite surprisingly showed an increased incidence of overall bone fractures among men who have received testosterone therapy compared to those who received placebo [1971]. However, it should be recognized that no difference in major osteoporotic fractures (i.e., hip, wrist, humerus, clinical spine and hip) were observed between groups. Moreover, this observation was derived from patient reports and therefore it deserves to be more specifically adjudicated. In conclusion, it should be recognized that the use of testosterone therapy as an adjunct to anti-resorptive treatment in hypogonadal patients at high risk of fractures has not been established. Therefore, anti-resorptive therapy must be the first-choice treatment in hypogonadal men at high risk for bone fractures. The combination of anti-resorptive treatment and testosterone therapy should be offered only in conjunction with hypogonadism-related symptoms.

3.4.2.6 Summary of evidence and recommendations for testosterone therapy outcome

Summary of evidence	**LE**
Testosterone therapy can improve:	
• Milder forms of ED and libido in hypogonadal men;	1a
• Other sexual symptoms, including intercourse frequency, orgasm and overall satisfaction.	1b
• Body composition and insulin resistance.	1a
• Weight, waist circumference and lipid profile, but the evidence is conflicting.	3
• Mild depressive symptoms in hypogonadal men.	1a
• Bone mineral density, but information related to fracture risk is lacking.	1a

Recommendations	**Strength rating**
Do not use testosterone therapy in eugonadal men.	Strong
Use testosterone therapy as first-line treatment in hypogonadal patients with mild erectile dysfunction (ED).	Strong
Use a combination of phosphodiesterase type 5 inhibitors and testosterone therapy in more severe forms of ED.	Weak
Use conventional medical therapies for severe depressive symptoms and osteoporosis.	Strong
Do not use testosterone therapy to reduce weight and enhance cardio-metabolic status.	Weak
Do not use testosterone therapy to improve cognition vitality and physical strength in ageing men.	Strong

3.4.3 Choice of treatment

3.4.3.1 Lifestyle factors

As reported above, functional hypogonadism is frequently associated with obesity and metabolic disorders [114]. Therefore, weight loss and lifestyle changes should be the first approach for all overweight and obese men with hypogonadism. A previous meta-analysis documented that a low-calorie diet can to revert obesity-associated secondary hypogonadism by increasing total testosterone and fT, reducing oestrogens and restoring normal gonadotropin circulating levels [115]. This was confirmed in an updated meta-analysis showing that the increase in testosterone is significantly associated with weight reduction [116]. Similar results can be obtained through physical activity, which is associated with the duration of scheduled exercise and weight loss obtained [116]. However, it should be recognised that the increase in testosterone levels observed after a low-calorie diet and physical activity is small (1-2 nmol) [115, 116]. In addition, 60-86% of weight lost is regained after three years and 75-121% after five years [117]. Lifestyle changes represent an essential part of the management of obesity; however, some evidence suggests that when compared to lifestyle modifications alone, testosterone therapy-treated obese men benefit most from relief of their symptoms associated with testosterone deficiency, whereas those not treated did not benefit [82]. There is limited evidence to suggest that combination of life-style interventions and testosterone therapy in symptomatic hypogonadal men might result in better outcomes [103]. As described above, the T4DM study has demonstrated that over two-years testosterone therapy with lifestyle intervention was superior to lifestyle intervention alone in reducing waist circumference and total and abdominal fat content. There was no significant reduction in body weight when compared to lifestyle intervention alone [33]. Interestingly, recent data also showed that weight loss obtained thought the use of Glucagon-like peptide-1 analogues analogues can result in better testosterone increases as compared with diet programs alone [1972].

3.4.3.2 Medical preparations

Several testosterone formulations are available (Table 5). Direct comparisons among different testosterone products are still lacking. Candidates for testosterone therapy should be adequately informed about the possible risks and benefits of all available testosterone preparations. The final choice should be based on the clinical situation, testosterone formulation availability, and patient needs and expectations [22, 118].

3.4.3.2.1 Oral formulations

An oral formulation has been available in oleic acid since the 1970s, and has been recently reformulated in a mixture of castor oil and propylene glycol laureate (testosterone undecanoate [TU] caps), to allow the drug to be maintained at room temperature without degradation [22, 118]. The main limitation is related to poor bioavailability, which is strongly dependent on dietary fat content [22, 118]. The US Food and Drug Administration (FDA) approved a new formulation of oral TU in a liquid-filled soft gel capsule, which improved oral availability [119]. Available evidence showed that TU capsule formulations can reach steady 24-hour average serum testosterone levels in more than 80% of hypogonadal men, thus resulting in a significant improvement of all sexual function domains at all time points when compared to baseline along with an excellent safety profile [119]. More recently, the FDA has approved a new oral formulation which contains as carriers Vitamin E, phytosterol esters, polyoxyl 40 hydrogenated castor oil and propylene glycol monolaurate [119]. For all new oral TU formulations a mild increase in arterial blood pressure has been reported. Hence, the FDA has required a black box warning that these drugs can induce a blood pressure increase [119].

Mesterolone is a 5α-dihydrotestosterone (DHT) derivate available for oral administration. Along with DHT, mesterolone cannot be converted to oestrogens and can only be used for a limited period and for specific indications, such as the presence of painful gynaecomastia. However, the lack of a full spectrum of testosterone bioactivity strongly limits its long-term use [22].

3.4.3.2.2 Parenteral formulations

Injectable testosterone preparations can be classified according to their half-lives (Table 5). Testosterone propionate is a short-term ester formulation requiring multiple fractionated doses (usually 50-100 mg, every two to three days), thus representing a major limitation for its use [22, 118]. Cypionate and enanthate-T esters are short-term formulations, requiring administration every two to four weeks. A formulation containing mixed testosterone esters (TU, isocaproate, phenyl propionate, propionate) which has the benefit of a steady release of testosterone into the circulation, is available in some countries. The use of these older formulations is associated with wide fluctuations in plasma testosterone concentrations and is often reported as unpleasant by patients potentially resulting in adverse effects, such as polycythaemia [22, 118, 120]. A longer-lasting TU injectable formulation is widely available [22, 118], with a good safety/benefit profile allowing the maintenance of normal stable testosterone levels at a dose of 1,000 mg initially every twelve weeks, following a six-week loading dose, but can be adjusted to a frequency of ten to fourteen weeks dependent on the trough (pre-injection level) after three to five injections to maintain levels in the therapeutic range (usually > 12 and < 18 nmol/L) [22, 118, 121].

3.4.3.2.3 Transdermal testosterone preparations

Among the available transdermal formulations, testosterone gels represent the most frequently used preparations. The gel is quickly absorbed by the stratum corneum, creating a reservoir within the subcutaneous tissues from where testosterone is continuously delivered for 24 hours, after a single daily application. These formulations have been shown to normalise serum testosterone levels with an excellent safety profile [22, 118]. The introduction of specific devices and skin enhancers has resulted in better skin penetration of the drugs, thus reducing potential adverse effects. Local skin adverse effects are limited when compared to those with traditional testosterone patches, but they potentially allow transference of testosterone during close contact with the skin surface. The risk can be reduced by wearing clothing or by applying the gel on skin surfaces not usually touched (e.g., the inner thigh surface) [22, 118]. To reduce the total amount of gel applied and residual quantities remaining on the skin, new formulations of testosterone gel have been introduced with a testosterone concentration of 1.62-2% [22, 118]. Another transdermal testosterone formulation includes a topical, alcohol-based testosterone (2%) solution, which must be applied to the underarm once daily, using a metered dose applicator [22, 118]. This testosterone formulation is not available in Europe. Testosterone levels should be monitored to optimise the testosterone dose. Blood collection is best taken two to four hours after gel application to use the peak level of testosterone absorbed as a reference for adequate therapeutic levels. Levels of testosterone after application can vary and a repeat measurement may be indicated especially as sometimes, inadvertently, the skin over the venipuncture site can be contaminated by the gel, leading to falsely elevated results.

In some European countries, DHT is available as a hydroalcoholic 2.5% gel. It is rapidly absorbed, reaching a steady state in two to three days [22, 118]. Similar to that reported for mesterolone, DHT is not aromatised but can be useful for treating particular conditions, such as gynaecomastia and microphallus [22, 118].

3.4.3.2.4 Transmucosal formulations

A testosterone buccal system is still available in several countries. It consists of a sustained-release muco-adhesive buccal-testosterone-tablet requiring twice-daily application to the upper gums. The tablet does not dissolve completely in the mouth and must be removed after twelve hours. This formulation has been proven to restore testosterone levels within the physiological range with minimal or transient local problems, including gum oedema, blistering and gingivitis [22, 118].

A gel for intranasal administration is available in some countries, including the USA and Canada. It requires administration two or three times daily using a specific metered-dose pump. The application is rapid, non-invasive, and convenient, and avoids secondary transference observed with other topical products [22, 118]. Preliminary results suggest that intranasal testosterone is associated with lower suppression of Gn levels and with a lower risk of haematocrit increases [122].

3.4.3.2.5 Subdermal depots

The implantation of testosterone pellets, available in a limited number of countries, represents the longest available testosterone formulation lasting from four to seven months. The procedure is invasive and may be unattractive to patients [22, 118].

3.4.3.2.6 Anti-oestrogens

Anti-oestrogens, including selective oestrogen receptor (ER) modulators (SERMs) and aromatase inhibitors (AI) have been suggested as off-label treatments to restore testosterone levels and fertility in men with functional secondary hypogonadism or idiopathic infertility. They work by preventing down-regulation of the HPG axis by oestrogens and for this reason are particularly useful in men with obesity and metabolic disorders [116, 123]. In the latter case, the hypothesis is that the excess of adipose tissue leads to increased aromatase activity and oestrogens levels resulting in impairment of the HPG [114]. Due to their putative mechanism of action, they require an intact HPG axis and cannot work in primary hypogonadism or secondary hypogonadism due to organic damage of the HPG axis. Both types of SERMs, which bind ERs with an agonist or antagonist effect depending upon the target tissue, and AIs, which prevent androgens from being converted into oestrogens by aromatase, have been used in clinical practice [22, 118]. The evidence published so far is poor; all these products are off-label treatments and SERMs, due to their agonistic effect on venous vessels, could predispose men to the development of venous thromboembolism [22, 118]. In this context patients should be warned of the potential increased risk of venous thromboembolism, although data are lacking. Long-term use of these agents can lead to reduced bone density and the development of osteoporosis, potentially increasing fracture risk.

3.4.3.2.7 Gonadotropins

Gonadotropin therapy should be considered the standard in men with secondary hypogonadism who desire paternity (Table 5) [22, 118]. Recombinant hCG (rhCG) and LH (rLH) formulations offer comparable effects to urinary-derived preparations [118]. According to a meta-analysis of the available evidence, hCG should be administered with FSH since combined therapy results in better outcomes. Similar to recombinant hCG, recombinant FSH (rFSH) offers comparable effects to urinary-derived preparations [121].

Table 5: Available preparations for hypogonadism treatment

Formulation	Chemical structure	t ½	Standard dosage	Advantages	Disadvantages
GONADOTROPINS					
Human chorionic gonadotrophin (HCG)					
Extractive	HCG purified from the urine of pregnant women	NA	1,000-2,000 IU 3 times/week	Low cost	Multiple weekly administration
Recombinant	Human recombinant HCG	NA	No data on men	NA	NA
Luteotropic hormone (LH)					
Recombinant	Human recombinant LH	NA	No data on men	NA	NA
Follicle-stimulating hormone (FSH)					
Extractive	FSH purified from urine of pregnant women	NA	75-150 IU 3 times/week	Low cost	Multiple weekly administration
Recombinant	Human recombinant FSH	NA	75-150 IU 3 times/week	NA	Multiple weekly administration
TESTOSTERONE PREPARATIONS					
Oral					
Testosterone undecanoate	17-α-hydroxylester	4 hours	120-240 mg 2-3 times daily	- Reduction of liver involvement - Oral convenience - Modifiable dosage	- Unpredictable absorption depending on dietary fat content - Must be taken with meals
Testosterone undecanoate self-emulsifying delivery system	17-α-hydroxylester	2-5 hours	100-237 mg 2 times daily	- Oral convenience - Modifiable dosage - Quick reversal	- Gastrointestinal side effects - increase in blood pressure
Mesterolone	1α-methyl-4, 5α-dihydro-testosterone	12 hours	50-100 mg 2-3 times daily	- Oral convenience - Modifiable dosage - Useful in gynaecomastia	- Not aromatisable
Parental					
Testosterone enanthate	17-α-hydroxylester	4-5 days	250 mg every 2-3 weeks	- Low cost - Short-acting preparation allowing drug withdrawal in case of adverse effects	- Fluctuations in circulating testosterone levels - Multiple injections - Relative risk of polycythemia
Testosterone cypionate	17-α-hydroxylester	8 days	200 mg every 2-3 weeks		
Testosterone propionate	17-α-hydroxylester	20 hours	100 mg every 2 days		
Testosterone ester mixture*	4-androsten-3-one-17 beta-hydroxy-androst-4-en-3-one	4-5 days	250 mg every 3 weeks		
Testosterone undecanoate in castor oil	17-α-hydroxylester	34 days	1,000 mg every 10-14 weeks *750 mg every 10 weeks	- Steady-state testosterone level without fluctuation - Long-lasting - Less frequent administration	- Pain at the injection site - Long-acting preparation not allowing rapid drug withdrawal in case of adverse effects

Surgical implants	Native testosterone	N/A	4-6 200 mg implants lasting up to 6 months	- Long duration and constant serum testosterone level	- Placement is invasive - Risk of extrusion and site infections
TRANSDERMAL					
Testosterone patches	Native testosterone	10 hours	50-100 mg/ day	Steady-state testosterone level without fluctuation	- Skin irritation - Daily administration
Testosterone gel 1-2%	Native testosterone	6 hours	50-100 mg/ day		- Possible transfer during intimate contact - Daily administration
Underarm testosterone (testosterone solution 2%)	Native testosterone	NA	60-120 mg/ day		
Dihydro-testosterone gel 2.5%	Native dihydro-testosterone	NA	34-70 mg/day	- Steady-state testosterone level without fluctuation - Useful in gynaecomastia	- Possible transfer during intimate contact - Daily administration - Not aromatisable
TRANSMUCOSAL					
Testosterone buccal system	Native testosterone	12 hours	60 mg 3 times daily	Steady-state testosterone level without fluctuation	- Possible oral irritation - Twice-daily dosing - Unpleasant taste
Testosterone nasal	Native testosterone	6 hours	33 mg 3 times daily		- Nasal irritation - Multiple daily administrations

NA = not applicable.
** Testosterone ester mixture - propionate (30mg), phenylpropionate (60mg), isocaproate (60mg), decanoate (100mg)*

3.4.3.2.8 Summary of evidence and recommendations for choice of treatment for LOH

Summary of evidence	**LE**
Weight loss obtained through a low-calorie diet and regular physical activity results in a small improvement in testosterone levels.	1a
Testosterone gels and long-acting injectable testosterone undecanoate preparations provide optimal safety profiles.	1a
Gonadotropin treatment can be used to restore fertility in men with secondary hypogonadism.	1a

Recommendations	**Strength rating**
Treat, when indicated, organic causes of hypogonadism (e.g., pituitary masses, hyperprolactinemia, etc).	Strong
Improve lifestyle and reduce weight (e.g., obesity); withdraw, when possible, concomitant drugs that can impair testosterone production; treat other co-morbidities, when possible, before starting testosterone therapy.	Strong
Fully inform patients about the expected benefits and adverse effects of any treatment option. Select the testosterone preparation in a joint decision process, and fully inform patients of the risks and benefits.	Strong
Use testosterone gels rather than long-acting depot administration when starting initial treatment in high-risk men.	Weak

3.5 Safety and follow-up in hypogonadism management

3.5.1 Hypogonadism and fertility issues

Pharmacological management of hypogonadism aims to increase testosterone levels to normal levels which resolve or improve symptoms of hypogonadism. The first choice is to administer exogenous testosterone. However, while exogenous testosterone has a beneficial effect on the clinical symptoms of hypogonadism, it temporarily inhibits gonadotropin secretion by the pituitary gland, resulting in impaired spermatogenesis and sperm cell maturation [124]. Therefore, testosterone therapy is contraindicated in hypogonadal men seeking fertility treatment [81]. When secondary hypogonadism is present, gonadotropin therapy may maintain normal testosterone levels and restore sperm production [3].

3.5.2 Male breast cancer

Studies have documented that breast cancer growth is significantly influenced by testosterone and/or by its conversion to oestradiol (E_2) through different mechanisms and pathways [125]. Accordingly, the use of SERMs still represents an important therapeutic option in the management of this cancer [125]. No information is available on the role of testosterone therapy in patients successfully treated for male breast cancer; therefore, treated and active male breast cancer should be recognised as absolute contraindications for testosterone therapy.

3.5.3 Lower urinary tract symptoms/benign prostatic hyperplasia (BPH)

A trial of 60 patients undergoing testosterone therapy for six months showed no significant differences on post-void residual urine and prostate volume, while storage symptoms as measured by IPSS significantly improved, despite an increase in prostate-specific antigen (PSA) level [126]. A larger pre-treatment prostate volume was a predictive factor of improvement in LUTS. Similarly, a placebo-controlled RCT including 120 hypogonadal (total testosterone < 12 nmol/L) men with MetS and listed for BPH surgery, showed that testosterone therapy did not result in a difference in LUTS severity compared to placebo. Conversely, an improvement in ultrasound markers of inflammation in the expression of several pro-inflammatory genes was found in the treatment active arm [127]. A long-term study of 428 men undergoing testosterone therapy for eight years demonstrated significant improvements in IPSS, no changes in max flow rate (Q_{max}) and residual urine volume, but also a significant increase in prostate volume [128]. Similar data from the Registry of Hypogonadism in Men (RHYME), including 999 patients with a follow-up of three years, did not demonstrate any significant difference in PSA levels or total IPSS in men undergoing testosterone therapy, compared to untreated patients [129]. Similar results were reported in an Italian registry (SIAMO-NOI), collecting data from 432 hypogonadal men from fifteen centres [130]. Meta-analyses have not found significant changes in LUTS between patients treated with testosterone or placebo [131-137]. According to the most recent literature, there are no grounds to discourage testosterone therapy in hypogonadal patients with BPH/LUTS and there is evidence of limited benefit from androgen administration. The only concern is related to patients with severe LUTS (IPSS > 19), as they are usually excluded from RCTs; therefore, limiting the long-term safety data of testosterone therapy in this specific setting [61].

3.5.4 Prostate cancer (PCa)

A considerable number of observational studies have failed to demonstrate any association between circulating higher testosterone levels and PCa [138]. In contrast, studies investigating the relationship between low levels of testosterone and risk of PCa have found that men with very low levels of fT have a reduced risk of developing low-to-intermediate-grade PCa, but have a non-significantly increased chance of developing high-grade PCa [138]. This peculiar pattern was also reported in trials such as the Health Professionals Follow-up Study, the Prostate Cancer Prevention Trial (PCPT) and the Reduction by Dutasteride of Prostate Cancer Events (REDUCE), with varying magnitudes of significance [139].

A meta-analysis, including 27 placebo-controlled, RCTs, found no evidence of increased PSA levels following testosterone therapy for one-year. When considering eleven studies reporting on the occurrence of PCa, the meta-analysis found no evidence of increased risk of PCa. However, a one year follow-up may be considered too short to draw firm conclusions on the risks of developing PCa. Furthermore, the analysis was restricted to studies with > 1-year follow-up, but no significant changes in PSA levels nor increased risk of PCa were found [132]. After five-year of median follow-up in three independent registry studies with > 1,000 patients undergoing testosterone therapy, PCa occurrence always remained below the reported incidence rate in the general population [140]. Similar results were reported by a large observational study including 10,311 men treated with testosterone therapy and 28,029 controls with a median follow-up of 5.3 years [141]. The same study, also showed that the risk of PCa was decreased for men in the highest tertile of testosterone therapy cumulative dose exposure as compared with controls [141].

Recently, the TRAVERSE study, a multicenter, randomized, double-blind, placebo-controlled, noninferiority trial involving 5246 men aged 45 to 80 years, who had pre-existing or a high risk of CVD and who have been

treated because of low testosterone levels (i.e., total T < 10.4 nmol/L) associated with reported symptoms of hypogonadism, did not show any difference in terms of PCa incidence or high-grade PCa rate between arms (testosterone therapy vs. placebo) at a mean follow-up, was 33.0± (SD) 12.1 months. Conversely, the same trial showed a significantly greater increase from baseline of total PSA in the treatment group as compared with the placebo arm [77].

With regards to PCa survivors, safety in terms of the risk of recurrence and progression has not yet been established. Limited data are available in the literature, with most case series not providing sufficient data to draw definitive conclusions (e.g., insufficient follow-up, small samples, lack of control arms, heterogeneity in study population and treatment regimen, etc.) [142]. A meta-analysis derived from thirteen studies including 608 patients, of whom 109 had a history of high-risk PCa, with follow-up of 1-189.3 months [143], suggested that testosterone therapy did not increase the risk of biochemical recurrence, but the available evidence is poor, limiting data interpretation [143]. Similar considerations can be derived from another, larger meta-analysis of 21 studies [144]. However, it is important to recognise both meta-analyses demonstrated high heterogeneity among the different studies and included a limited number of subjects. An RCT assessing the safety/benefit ratio of testosterone therapy in hypogonadal men successfully treated with prostatectomy for non-aggressive prostate PCa is currently ongoing [145].

In conclusion, recent literature does not support an increased risk of PCa in hypogonadal men undergoing testosterone therapy. Although it is mandatory to avoid testosterone administration in men with advanced PCa, insufficient long-term prospective data on the safety of testosterone therapy in PCa survivors [144], should prompt caution in choosing to treat symptomatic hypogonadal men in this setting. In particular, patients should receive comprehensive counselling regarding the uncertain long-term effects of testosterone therapy in this context, which necessitates further investigation. Due to the lack of strong evidence-based data on safety, the possible use of testosterone therapy in symptomatic hypogonadal men previously treated for PCa should be fully discussed with patients and limited to low-risk individuals.

3.5.5 ***Cardiovascular Disease***

Evidence suggests that hypogonadal men have an increased risk of CVD [146, 147]. Whether or not LOH is a cause or a consequence of atherosclerosis has not been clearly determined. Late-onset hypogonadism is associated with CV risk factors, including central obesity, insulin resistance and hyperglycaemia, dyslipidaemia, pro-thrombotic tendency and chronic inflammatory state [147]. Atherosclerosis is a chronic inflammatory disease, that releases pro-inflammatory cytokines into the circulation, which are known to suppress testosterone release from the HPG axis. Evidence from RCTs of testosterone therapy in men with MetS and/or T2DM demonstrates some benefit in CV risk, including reduced central adiposity, insulin resistance, total cholesterol and LDL-cholesterol and suppression of circulating cytokines [28-30, 35, 147, 148]. However, due to the equivocal nature of these studies, testosterone therapy cannot be recommended for use outside of treatment of specific symptoms.

Published data show that LOH is associated with an increase in all-cause and CVD-related mortality [7, 149-152]. These studies are supported by a meta-analysis that concluded that hypogonadism is a risk factor for cardiovascular morbidity [136] and mortality [153]. Importantly, men with low testosterone when compared to eugonadal men with angiographically proven coronary disease have twice the risk of earlier death [147]. Longitudinal population studies have reported that men with testosterone in the upper quartile of the normal range have a reduced number of CV events compared to men with testosterone in the lower three quartiles [149]. Androgen deprivation therapy for PCa is linked to an increased risk of CVD and sudden death [154]. Conversely, two long-term epidemiological studies have reported reduced CV events in men with high normal serum testosterone levels [155, 156]. Erectile dysfunction is independently associated with CVD and may be the first clinical presentation in men with atherosclerosis.

The knowledge that men with hypogonadism and/or ED may have underlying CVD should prompt individual assessment of their CV risk profile. Individual risk factors (e.g., lifestyle, diet, exercise, smoking, hypertension, diabetes and dyslipidaemia) should be assessed and treated in men with pre-existing CVD and in patients receiving androgen deprivation therapy. Cardiovascular risk reduction can be managed by primary care clinicians, but patients should be appropriately counselled by clinicians active in prescribing testosterone therapy [83]. If appropriate, patients should be referred to cardiologists for risk stratification and treatment of comorbidity.

No RCTs have provided a clear answer on whether testosterone therapy affects CV outcomes. The TTrial (n=790) conducted in older men [157], the TIMES2 study (n=220) [29], along with the BLAST studies involving men with Metabolic Syndrome (MetS) and Type 2 Diabetes Mellitus (T2DM), as well as the study involving pre-frail and frail

elderly men - all of which lasted for one year, and the T4DM study spanning two years - did not show any increase in Major Adverse Cardiovascular Events (MACE) increase in Major Adverse Cardiovascular Events (MACE) [29, 32, 33, 157, 158]. Randomised controlled trials, between three and twelve months, in men with known heart disease treated with testosterone have not found an increase in MACE, but have reported improvement in cardiac ischaemia, angina and functional exercise capacity [159-161]. A large cohort study (n=20,4857 men) found that neither transdermal gel or intramuscular testosterone was associated with an increased risk of composite cardiovascular outcome in men with or without prevalent CVD (mean follow-up 4.3 years) [162]. The European Medicines Agency (EMA) has stated that 'The Co-ordination Group for Mutual recognition and Decentralisation 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 in men. 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 drugs [163].

Data recently released from the TRAVERSE study confirm the findings of the EMA [77]. The latter is the first double-blind, placebo-controlled, non-inferiority RCT with primary CV safety as an end point. The results showed that testosterone therapy was noninferior to placebo with respect to the incidence of MACE. However, a mild higher incidence of atrial fibrillation, acute kidney injury, and pulmonary embolism was observed in the testosterone group [77]. The latter observations, however, need to be confirmed since previous available data do not support an increased risk of venous thromboembolism [78, 164] or major arrhythmias [165] after testosterone therapy. Similarly, the long-term follow-up (median of 5.1 years since last injection) of the T4DM study showed no differences in self-reported rates of new diagnosis of CVD [166].

In conclusion, current available data from interventional studies suggest that there is no increased risk up to three years of testosterone therapy [167-171]. The currently published evidence has reported that testosterone therapy in men with diagnosed hypogonadism has neutral or beneficial actions on MACE in patients with normalised testosterone levels. The findings could be considered sufficiently reliable for at least a three year course of testosterone therapy, after which no available study can exclude further or long-term CV events [172, 173].

3.5.5.1 Cardiac Failure

Testosterone therapy is contraindicated in men with severe chronic cardiac failure because fluid retention may lead to exacerbation of the condition. Some studies have shown that men with moderate chronic cardiac failure may benefit from low doses of testosterone, which achieve mid-normal range testosterone levels [160, 174, 175]. An interesting observation is that untreated hypogonadism increased the re-admission and mortality rate in men with heart failure [176]. If a decision is made to treat hypogonadism in men with chronic cardiac failure, it is essential that the patient is followed up carefully with clinical assessment and both testosterone and haematocrit measurements on a regular basis.

*3.5.6 **Erythrocytosis***

An elevated haematocrit level is the most common adverse effect of testosterone therapy. Stimulation of erythropoiesis is a normal biological action that enhances the delivery of oxygen to testosterone-sensitive tissues (e.g., striated, smooth and cardiac muscle). Any elevation above the normal range for haematocrit usually becomes evident between three and twelve months after testosterone therapy initiation. However, polycythaemia can also occur after any subsequent increase in testosterone dose, switching from topical to parenteral administration and, development of comorbidity, which can be linked to an increase in haematocrit (e.g., respiratory or haematological diseases).

There is no evidence that an increase of haematocrit up to and including 54% causes any adverse effects. If the haematocrit exceeds 54% there is a testosterone independent, but weak associated rise in CV events and mortality [79, 177-179]. Any relationship is complex as these studies were based on patients with any cause of secondary polycythaemia, which included smoking and respiratory diseases. There have been no specific studies in men with only testosterone-induced erythrocytosis.

As detailed, the TRAVERSE study, which had included symptomatic hypogonadal men aged 45-80 years who had pre-existing or a high risk of CVD, showed a mild higher incidence of pulmonary embolism, a component of the adjudicated tertiary end point of venous thromboembolic events, in the testosterone therapy than in the placebo group (0.9% vs. 0.5%) [77]. However, three previous large studies have not shown any evidence that testosterone therapy is associated with an increased risk of venous thromboembolism [180, 181]. Of those, one study showed that an increased risk peaked at six months after initiation of testosterone therapy, and then declined over the subsequent period [182]. In one study venous thromboembolism was reported in 42 cases

and 40 of these had a diagnosis of an underlying congenital thrombophilia (including factor V Leiden deficiency, prothrombin mutations and homocysteinuria) [183]. A meta-analysis of RCTs of testosterone therapy reported that venous thromboembolism was frequently related to underlying undiagnosed thrombophilia-hypofibrinolysis disorders [78]. In an RCT of testosterone therapy in men with chronic stable angina there were no adverse effects on coagulation, by assessment of tissue plasminogen activator or plasminogen activator inhibitor-1 enzyme activity or fibrinogen levels [184]. Similary, another meta-analysis and systematic review of RCTs found that testosterone therapy was not associated with an increased risk of venous thromboembolism [164]. With testosterone therapy elevated haematocrit levels are more likely to occur if the baseline level is toward the upper limit of normal prior to initiation. Added risks for raised haematocrit on testosterone therapy include smoking or respiratory conditions at baseline. Higher haematocrit is more common with parenteral rather than topical formulations. Accordingly, a large retrospective two-arm open registry, comparing the effects of long-acting testosterone undecanoate and testosterone gels showed that the former preparation was associated with a higher risk of haematocrit levels > 50%, when compared to testosterone gels [185]. In men with pre-existing CVD extra caution is advised with a definitive diagnosis of hypogonadism before initiating testosterone therapy and monitoring of testosterone as well as haematocrit during treatment.

Elevated haematocrit in the absence of comorbidity or acute CV or venous thromboembolism can be managed by a reduction in testosterone dose, change in formulation or if the elevated haematocrit is very high by venesection (500 mL), even repeated if necessary, with usually no need to stop the testosterone therapy.

*3.5.7 **Obstructive Sleep Apnoea***

There is no evidence that testosterone therapy can result in the onset or worsening of sleep apnoea. Combined therapy with Continuous Positive Airway Pressure (CPAP) and testosterone gel was more effective than CPAP alone in the treatment of obstructive sleep apnoea [186]. In one RCT, testosterone therapy in men with severe sleep apnoea reported a reduction in oxygen saturation index and nocturnal hypoxaemia after seven weeks of therapy compared to placebo, but this change was not evident after eighteen weeks' treatment and there was no association with baseline testosterone levels [187].

*3.5.8 **Follow-up***

Testosterone therapy alleviates symptoms and signs of hypogonadism in men in a specific time-dependent manner. The TTrials clearly showed that testosterone therapy improved sexual symptoms as early as three months after initiation [93]. Similar results have been derived from meta-analyses [78, 85]. Hence, the first evaluation should be planned after three months of treatment. Further evaluation may be scheduled at six months or twelve months, according to patient characteristics, as well as results of biochemical testing (see below). Patients at high risk of developing elevated haematocrit should be evaluated every three months during the first year of testosterone therapy and at least every six months thereafter. Accordingly, current guidelines suggest that haematocrit should be maintained below 45% in patients with polycythaemia vera to avoid thromboembolism risk [188]. Similarly, data derived using a multi-institutional database including a large cohort of hypogonadal (total testosterone < 12 nmol/L) men who received testosterone therapy and subsequently did (n=5,887) or did not (n=4,2784) develop polycythaemia (haematocrit > 52%) showed that men who had an increased haematocrit had a higher risk of MACE or venous thromboembolism mostly during the first year of therapy [189]. The risk was even higher when a haematocrit threshold of 54% was considered whilst no risk was observed when a 50% threshold was applied [189]. Table 6 summarises the clinical and biochemical parameters that should be monitored during testosterone therapy.

TTrials were designed to maintain the serum testosterone concentration within the normal range for young men (280–873 ng/dL or 9.6-30 nmol/L) [93]. This approach resulted in a good benefit/risk ratio. A similar approach could be considered during follow-up. The correct timing for the evaluation of testosterone levels varies according to the type of preparation used (Table 5). Testosterone is involved in the regulation of erythropoiesis [120] and prostate growth [61], hence evaluation of PSA and haematocrit should be mandatory before and during testosterone therapy. However, it is important to recognise that the risk of PCa in men aged < 40 years is low. Similarly, the mortality risk for PCa in men aged > 70 years has not been considered high enough to warrant monitoring in the general population [190]. Therefore, any screening for PCa through the determination of PSA and DRE in men aged < 40 or > 70 years during testosterone therapy should be discussed with the patients.

Baseline and, at least, annual glyco-metabolic profile evaluation may be a reasonable consideration, particularly in the management of functional hypogonadism. Testosterone therapy may be beneficial for hypogonadal men with low or moderate fracture risk [107]; therefore, dual energy X-ray absorptiometry (DEXA) bone scan may also be considered at baseline and 18-24 months following testosterone therapy, particularly in patients with more severe hypogonadism [107].

Digital rectal examination may detect prostate abnormalities that can be present even in men with normal PSA values. Hence, DRE is mandatory in all men at baseline and is recommended to be performed at least annually during testosterone therapy, as long as there is no significant increase in PSA velocity.

The decision to stop testosterone therapy or to perform a prostate biopsy due to PSA increase or prostate abnormalities should be based on local PCa guidelines. There is a large consensus that any increase of haematocrit > 54% during testosterone therapy requires therapy withdrawal and phlebotomy to avoid potential adverse effects including venous-thromboembolism and CVD, especially in high-risk individuals. In patients with lower risk of relevant clinical sequelae, the situation can be alternatively managed by reducing testosterone dose and switching formulation along with venesection. A positive family history of venous-thromboembolism should be carefully investigated and the patient counselled about testosterone therapy to avoid/prevent thrombophilia-hypofibrinolysis [78]. Finally, caution should be exercised in men with pre-existing CVD or at higher risk of CVD [77].

Table 6: Clinical and biochemical parameters to be checked during testosterone therapy

Parameters		Year 1 of treatment			After year 1 of treatment	
	Baseline	3 months	6 months	12 months	Annually	18-24 months
Clinical						
Symptoms	X	X	X	X	X	
Body Mass Index	X			X	X	
Waist circumference	X	X		X	X	
Digital rectal examination	X			X	X	
Blood pressure	X	X		X	X	
Biochemistry						
PSA (ng/mL)	X	X	X[2]	X	X	
Haematocrit (%)	X	X	X[1,2]	X	X	
Testosterone	X	X		X	X	
Lipid and glycaemic profile	X			X	X	
Instrumental						
DEXA	X					X

[1]Population with polycythaemia vera or at high risk of secondary polycythaemia (e.g., sleep apnea, morbid obesity, heavy smokers, chronic obstructive pulmonary disease); [2]Prostate cancer survivors.

3.5.9 Summary of evidence and recommendations on safety and monitoring in testosterone treatment

Summary of evidence	LE
Testosterone therapy is contraindicated in men with secondary hypogonadism who desire fertility.	1a
Testosterone therapy is contraindicated in men with active prostate cancer or breast cancer, as these patients are usually excluded from RCTs.	1a
Testosterone therapy does not increase the risk of prostate cancer, but long-term prospective follow-up data are required to validate this statement.	1a
The effect of testosterone therapy in men with severe lower-urinary tract symptoms is limited, as these patients are usually excluded from RCTs.	1a
There is no substantive evidence that testosterone therapy, when replaced to normal levels, results in the development of major adverse cardiovascular events.	1a
There is no evidence of a relationship between testosterone therapy and mild, moderate or CPAP-treated severe sleep apnoea.	1b

Recommendations	Strength rating
Fully counsel symptomatic hypogonadal men who have been surgically treated for localised prostate cancer (PCa) and who are currently without evidence of active disease considering testosterone therapy, emphasising the lack of sufficient safety data on long-term follow-up.	Weak
Restrict treatment to patients with a low risk of recurrent PCa*. Treatment should start after at least one year of follow-up with prostate-specific antigen (PSA) level < 0.01 ng/mL.	Weak
Advise patients that safety data on the use of testosterone therapy in men treated for breast cancer are unknown.	Strong
Assess cardiovascular risk factors before commencing testosterone therapy.	Strong
Assess men with known cardiovascular disease (CVD) for cardiovascular symptoms before initiating testosterone therapy and monitor these men with close clinical assessment and evaluation during treatment.	Strong
Treat men with hypogonadism and pre-existing CVD, venous-thromboembolism or chronic cardiac failure, who require testosterone therapy with caution, by careful clinical monitoring and regular measurement of haematocrit (not exceeding 54%) and testosterone levels.	Weak
Exclude a family history of venous-thromboembolism before starting testosterone therapy.	Strong
Monitor testosterone, and haematocrit at three, six and twelve months after testosterone therapy initiation, and thereafter annually. A haematocrit > 54% requires testosterone therapy adjustment or withdrawal and venesection if required. Re-introduce testosterone therapy at a lower dose once the haematocrit has normalised and consider switching to topical testosterone preparations.	Strong
Evaluate patients with polycythaemia vera and those with a higher risk of developing elevated haematocrit every three months during the first year of testosterone therapy, and at least every six months thereafter.	Strong
Evaluate total PSA in PCa survivors at three, six and twelve months during the first year of testosterone therapy, and annually thereafter.	Strong

**As for EAU risk groups for biochemical recurrence of localised or locally advanced prostate cancer (see EAU Prostate Cancer Guidelines, 2024)*

4. EPIDEMIOLOGY AND PREVALENCE OF SEXUAL DYSFUNCTION AND DISORDERS OF MALE REPRODUCTIVE HEALTH

4.1 Erectile dysfunction

Epidemiological data have shown a high prevalence and incidence of ED worldwide [191]. Among others, the Massachusetts Male Aging Study (MMAS) [192] 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% [193]. The incidence rate of ED (new cases per 1,000 men annually) was 26 in the long-term data from the MMAS study [194] and 19.2 (mean follow-up of 4.2 years) in a Dutch study [195]. In a cross-sectional real-life study among men seeking first medical help for new-onset ED, one in four patients were younger than 40 years, with almost 50% of the young men complaining of severe ED [196]. Differences among these studies can be explained by differences in methodology, ages, and socio-economic and cultural status of the populations studied. The prevalence rates of ED studies are reported in Table 1 online supplementary evidence: https://uroweb.org/guidelines/sexual-and-reproductive-health/publications-appendices.

4.2 Premature ejaculation

The highest prevalence rate of 31% (men aged 18-59 years) was found by the National Health and Social Life Survey (NHSLS), which determines adult sexual behaviour in the USA [197]. Prevalence rates were 30% (18-29 years), 32% (30-39 years), 28% (40-49 years) and 55% (50-59 years), respectively. However, it is unlikely that the premature ejaculation (PE) prevalence is as high as 20-30% based on the relatively low number of men

who seek medical help for 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 [198]. Two separate observational, cross-sectional surveys from different continents found that the overall prevalence of PE was 19.8 and 25.8%, respectively [199, 200]. Further stratifying these complaints into the classifications defined by Waldinger *et al.*, [201], rates of lifelong PE were 2.3 and 3.18%, acquired PE 3.9 and 4.48%, variable PE 8.5 and 11.38% and subjective PE 5.1 and 6.4%, respectively [199, 200]. Both studies showed that men with acquired PE were more likely to seek treatment compared to men with lifelong PE. The prevalence rates of premature ejaculation as evidenced by the highly discrepant prevalence rates reported in Appendix 2 online supplementary evidence: https://uroweb.org/guidelines/sexual-and-reproductive-health/publications-appendices.

4.3 Other ejaculatory disorders

4.3.1 ***Delayed ejaculation***

Due to its rarity and uncertain definitions, the epidemiology of delayed ejaculation (DE) is not clear [202]. However, several well-designed epidemiological studies have revealed that its prevalence is around 3% among sexually active men [197, 203]. According to data from the NHSLS, 7.78% of a national probability sample of 1,246 men aged 18-59 years reported an inability to achieve climax or ejaculation [197]. In a similar stratified national probability sample survey completed over six months among 11,161 men and women aged 16-44 years in Britain, 0.7% of men reported an inability to reach orgasm [204]. In an international survey of sexual problems among 13,618 men aged 40–80 years from 29 countries, 1.1-2.8% of men reported that they frequently experience inability to reach orgasm [205]. Another study conducted in the United States (USA), in a national probability sample of 1,455 men aged 57-85 years, 20% of men reported an inability to climax and 73% reported that they were bothered by this problem. [206]. Similar to PE, there are distinctions among lifelong, acquired and situational DE [207]. Although the evidence is limited, the prevalence of lifelong and acquired DE is estimated at 1 and 4%, respectively [208].

4.3.2 ***Anejaculation and Anorgasmia***

Establishing the exact prevalence of anejaculation and anorgasmia is difficult since many men cannot distinguish between ejaculation and orgasm. The rarity of these clinical conditions further hampers the attempts to conduct epidemiological studies. In a report from the USA, 8% of men reported unsuccessfully achieving orgasm during the past year [197].

According to Kinsey *et al.*, [209], 0.14% of the general population has anejaculation. The most common causes of anejaculation were spinal cord injury, diabetes mellitus and multiple sclerosis. Especially in most cases of spinal cord injury, medical assistance is the only way to ejaculate. While masturbation leads to the lowest rates of ejaculation, higher response rates can be obtained with penile vibratory stimulation or acetylcholine esterase inhibitors followed by masturbation in patients with spinal cord injury [210].

4.3.3 ***Retrograde ejaculation***

Similar to anejaculation, it is difficult to estimate the true incidence of retrograde ejaculation (RE). Although RE is generally reported in 0.3-2% of patients attending fertility clinics [211], diabetes may increase these rates by leading to autonomic neuropathy. Autonomic neuropathy results in ED and ejaculatory dysfunctions ranging from DE to RE and anejaculation, depending on the degree of sympathetic autonomic neuropathy involved [212]. In 54 diabetic patients with sexual dysfunction, RE was observed with a 6% incidence [213]. In a controlled trial, RE was observed in 34.6% of diabetic men [214]. A trial reported the rate of RE among 57 type-1-diabetes mellitus patients (aged 18-50 years) was at least 8.8% [215]. Retrograde ejaculation was also reported in studies of patients who had undergone transurethral resection of prostate (TURP) or open prostatectomy due to disrupted bladder neck integrity. A study of the effect of prostatectomy on QoL in 5,276 men after TURP, found that 68% reported post-surgical RE [216]. However, with the development of less invasive techniques, the incidence of RE decreases following the surgical treatment of LUTS [217-221].

4.3.4 ***Painful ejaculation***

Painful ejaculation is a common but poorly understood clinical phenomenon, which is associated with sexual dysfunction. Several studies demonstrated its prevalence to range between 1-10% in the general population [222-224]; however, it may increase to 30-75% among men with chronic prostatitis/chronic pelvic pain syndrome (CP/CPPS) [225-229]. It should be noted that the design of most of these studies was not scientifically sound and the condition was probably under-reported due to the lack of an evidence-based definition and well-defined prognostic criteria.

*4.3.5 **Haemospermia***

The exact incidence and prevalence of haemospermia is difficult to elucidate due to a number of factors including its covert presentation, usually self-limiting nature and patient embarrassment. The symptoms represent 1-1.5% of all urological referrals and occur in all age groups, with a mean age of 37 years [230, 231]. In a PCa screening study of 26,126 men, aged ≥ 50 years or older than 40 with a history of PCa or of black ethnicity, haemospermia was found in 0.5% on entry to the trial [232].

4.4 Low sexual desire

The global prevalence of low sexual desire in men is 3-28% [205, 233, 234]. Low solitary and dyadic sexual desires have been reported in 68% and 14% of men, respectively [235]. Also, low sexual desire has been observed as a common complaint in gay men, with a prevalence of 19-57% [236, 237]. Despite its relationship with age, low sexual desire has also been reported among young men (18-29 years), with a prevalence of 6-19% [197, 238, 239].

5. MANAGEMENT OF ERECTILE DYSFUNCTION

5.1 Definition and classification

Erectile dysfunction (ED) is defined as the persistent inability to attain and maintain an erection sufficient to permit satisfactory sexual performance [240]. Erectile dysfunction may affect psychosocial health and have a significant impact on the QoL of patients and their partner's [192, 241-243]. Erectile dysfunction is commonly classified into three groups based on aetiology: organic, psychogenic and mixed ED. However, this classification should be used, with caution as most cases are actually of mixed aetiology. It has therefore been suggested to use the terms "primary organic" or "primary psychogenic".

5.2 Risk factors

Erectile dysfunction is associated with numerous risk factors including age, diabetes mellitus, dyslipidaemia, hypertension, CVD, obesity, MetS, hyperhomocysteinemia, lack of exercise, smoking and drug use [242, 244-255]. In addition, several therapeutic agents for CVD have been shown to have a detrimental effect on erectile function (EF), whereas newer drugs have exhibited a neutral or even beneficial effect [247, 256, 257]. Other reported risk factors include atrial fibrillation, hyperthyroidism, vitamin D and folic acid deficiency, hyperuricemia, depression and anxiety disorders, chronic kidney and rheumatic disease, COPD, migraine, inflammatory bowel disease and osteoporosis [252, 258-270]. In addition, a growing body of evidence has demonstrated an association between the onset of new ED in men who have had COVID-19 [1974-1976].

Erectile dysfunction is also frequently associated with other urological conditions and procedures including LUTS/BPH and surgery for LUTS/BPH [275-277], chronic pelvic pain syndrome (CPPS) and chronic prostatitis [278], bladder pain syndrome/interstitial cystitis [279], premature ejaculation [280] and urethroplasty surgery for posterior urethral strictures [281].

5.3 Pathophysiology

The pathophysiology of ED may be vasculogenic, neurogenic, anatomical, hormonal, drug-induced and/or psychogenic (Table 7) [282]. In most cases, numerous pathophysiological pathways can co-exist and may all negatively impact EF.

Table 7: Urological conditions associated with ED [282]

Vasculogenic
Recreational habits (i.e., cigarette smoking)
Lack of regular physical exercise
Obesity
Cardiovascular diseases (e.g., hypertension, coronary artery disease, peripheral vasculopathy)
Type 1 and 2 diabetes mellitus; hyperlipidaemia; metabolic syndrome; hyperhomocysteinemia
Major pelvic surgery (e.g., radical prostatectomy) or radiotherapy (pelvis or retroperitoneum)

Neurogenic
Central causes
Degenerative disorders (e.g., 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, chronic liver failure
Polyneuropathy
Surgery (major surgery of pelvis/retroperitoneum) or radiotherapy (pelvis or retroperitoneum)
Surgery of the urethra (urethral stricture, open urethroplasty, etc.)
Anatomical or structural
Hypospadias, epispadias; micropenis
Phimosis
Peyronie's disease
Penile cancer (other tumours of the external genitalia)
Hormonal
Diabetes mellitus; Metabolic Syndrome (MeTS)
Hypogonadism (any type)
Hyperthyroidism
Hyper- and hypocortisolism (Cushing's disease, etc.)
Panhypopituitarism and multiple endocrine disorders
Mixed pathophysiological pathways
Chronic systemic diseases (e.g., diabetes mellitus, hypertension, MeTS, chronic kidney disease, chronic liver disorders, hyperhomocysteinemia, hyperuricemia, chronic obstructive pulmonary disease, rheumatic disease)
Psoriasis, gouty arthritis, ankylosing spondylitis, non-alcoholic fatty liver disease, chronic periodontitis, open-angle glaucoma, inflammatory bowel disease, chronic fatigue syndrome, allergic rhinitis, obstructive sleep apnoea, depression
Iatrogenic causes (e.g. TRUS-guided prostate biopsy)
Drug-induced
Antihypertensives (i.e., thiazidediuretics, beta-blockers)*
Antidepressants (e.g., selective serotonin reuptake inhibitors, tricyclics)
Antipsychotics
Antiandrogens (GnRH analogues and antagonists; 5-ARIs)
Recreational drugs (e.g., heroin, cocaine, marijuana, methadone, synthetic drugs, anabolic steroids, excessive alcohol intake)
Psychogenic
Generalised type (e.g., lack of arousal and disorders of sexual intimacy)
Situational type (e.g., partner-related, performance-related issues or due to distress)
Trauma
Penile fracture
Pelvic fracture

GnRH = gonadotropin-releasing hormone; 5-ARIs = 5α-reductase inhibitors.
**A symmetry analysis showed that cardiovascular drugs do not strongly affect the risk of subsequently being prescribed as an anti-erectogenic drug. The analysis only assessed the short-term risk [283].*

5.3.1 Pelvic surgery and prostate cancer treatment

Pelvic surgery, especially for oncological disease (e.g., radical prostatectomy (RP) [284], radical cystectomy [285] and colorectal surgery [286]), may have a negative impact on EF and overall sexual health. Surgery resulting in damage of the neurovascular bundles, that control the complex mechanism of the cavernous erectile response, may result in ED, although NS approaches have been adopted over the last few decades. To date only the surgical treatment of PCa has enough scientific evidence supporting its potential pathophysiological association with ED [287-289]. However, even non-surgical treatments of PCa (i.e., radiotherapy, or brachytherapy) can be associated with ED [287, 290, 291].

The ProtecT trial randomised 1,643 patients to active treatment (RP or RT) or active monitoring for localised PCa and assessed sexual function, including EF, using the EPIC-26 instrument [271]. At baseline, 67% of men reported erections firm enough for sexual intercourse. At the six year follow-up assessment this fell to 30% in the active monitoring group, 27%% in the RT group and 17% in the RP group, respectively.

Radical prostatectomy for the treatment of clinically localised intermediate- or high-risk PCa is a widely performed procedure. Research has shown that 25-75% of men experience post-RP ED [272, 273, 288]. Conversely, the rate of unassisted post-operative EF recovery ranges between 20 and 25% in most studies. These rates have not substantially improved or changed over the past seventeen years, despite growing attention to post-surgical rehabilitation protocols and refinement of surgical techniques [273, 274, 292]. Overall, patient age, baseline EF and surgical volume, with the subsequent ability to preserve the neurovascular bundles, are the main factors in promoting the highest rates of post-operative EF [272, 289, 293, 294]. Regardless of the surgical technique, surgeons' experience clearly impacts on post-operative EF outcome [295]. The surgical approach may also affect post-RP EF, but the current evidence conflicts with one systematic review reporting a significant advantage in favour of RARP compared to open retropubic RP for twelve-month potency rates [296] and two RCTs reporting only a small improvement in EF for RARP or no different in EF between techniques [297, 298].

Erectile dysfunction is also a common problem after both external beam radiation therapy (EBRT) and brachytherapy for PCa. A systematic review and meta-analysis including men treated with EBRT (65%), brachytherapy (31%) or both (4%) showed that the post-treatment prevalence of ED was 34% at one year and 57% at 5.5 years, respectively [299, 300]. Similar findings have been reported for stereotactic radiotherapy with 26-55% of previously sexually functioning patients reporting ED at five years [301].

Recently other modalities have emerged as potential therapeutic options in patients with clinically-localised PCa, including high-intensity focused US (HIFU), cryo-therapeutic ablation of the prostate (cryotherapy), focal padeliporfin-based vascular-targeted photodynamic therapy and focal RT by brachytherapy or CyberKnife®. All these approaches have been reported to have a less-negative impact on EF with many studies reporting a complete recovery at one-year follow-up [302].

5.3.2 Summary of evidence on the epidemiology/aetiology/pathophysiology of ED

Summary of evidence	LE
Erectile dysfunction is common worldwide.	2b
Erectile dysfunction shares common risk factors with cardiovascular disease.	2b
Lifestyle modification (regular exercise and decrease in BMI) can improve erectile function.	1b
Erectile dysfunction 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
Erectile dysfunction is common after RP, irrespective of the surgical technique used.	2b
Erectile dysfunction is common after external radiotherapy and brachytherapy.	2b
Erectile dysfunction is less common after cryotherapy and high-intensity focused US.	2b

5.4 Diagnostic evaluation (basic work-up)

5.4.1 Medical and sexual history

The first step in evaluating ED is always a detailed medical and sexual history of patients and, when available, their partners [303]. Figure 2 lists the minimal diagnostic evaluation (basic work-up) in patients with ED.

A detailed description should be made of the rigidity and duration of both sexually-stimulated and morning erections and problems with sexual desire, arousal, ejaculation, and orgasm [304-306]. Validated psychometric questionnaires, such as the IIEF [307] or its short version (i.e., Sexual Health Inventory for Men; SHIM) [308], help to assess the different sexual function domains (i.e. sexual desire, EF, orgasmic function, intercourse satisfaction, and overall satisfaction), as well as the potential impact of a specific treatment modality. Similarly, structured interviews allow the identification and quantification of the different underlying factors affecting EF [309].

Psychometric analyses also support the use of the Erectile Hardness Score (EHS) for the assessment of penile rigidity in practice and clinical trials research [310].

Patients should always be screened for symptoms of possible hypogonadism, including decreased libido and energy, and fatigue (see Table 3: Specific symptoms associated with LOH).

*5.4.2 **Physical examination***

Every patient must be given a physical examination focused on the genitourinary, endocrine, vascular and neurological systems [311, 312]. A physical examination may reveal unsuspected diagnoses, such as Peyronie's disease (PD), pre-malignant or malignant genital lesions, prostatic enlargement or irregularity/nodularity, or signs and symptoms suggestive of hypogonadism (see Table 3: Specific symptoms associated with LOH).

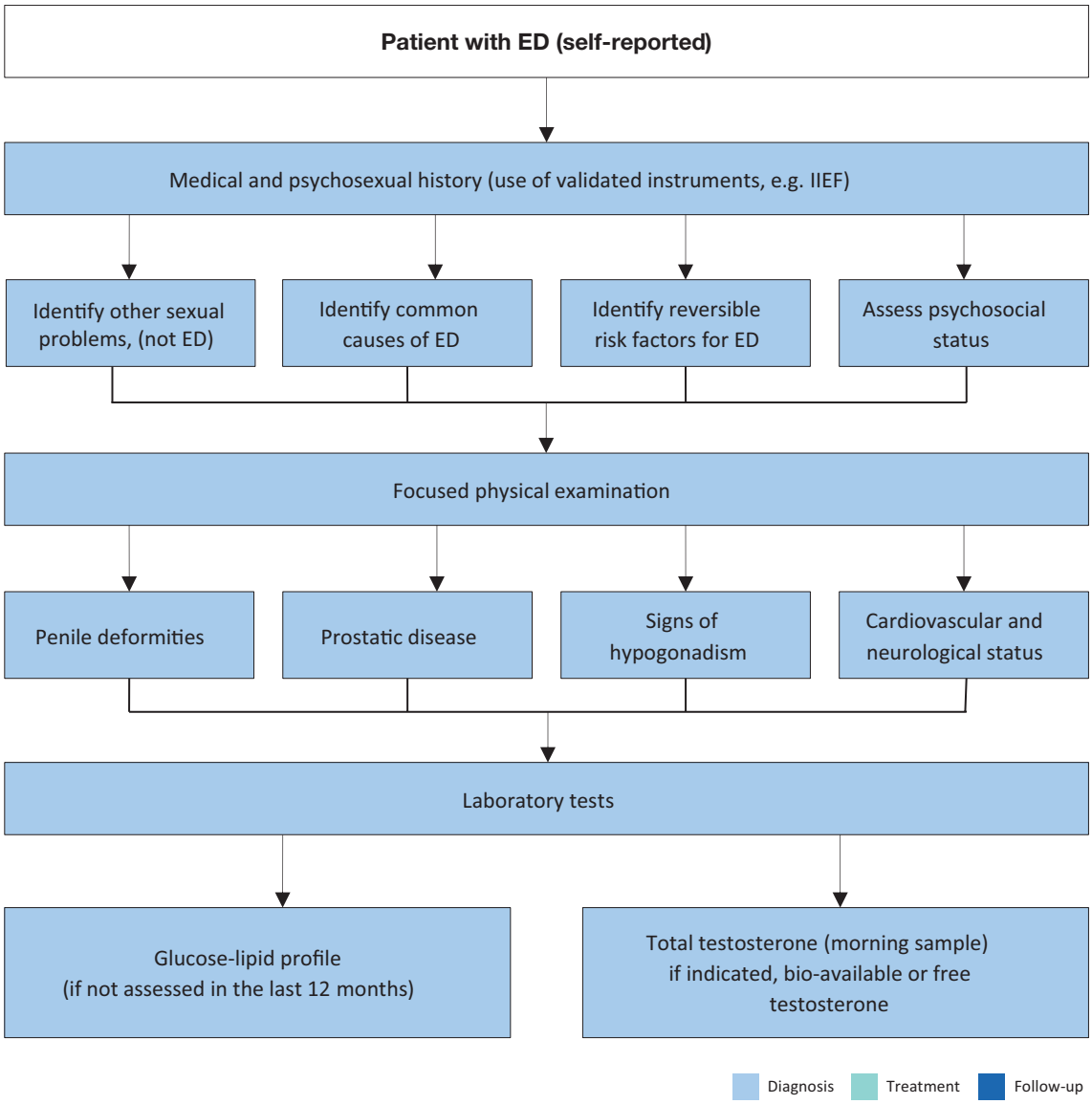
Blood pressure and heart rate should be measured if they have not been assessed in the previous three to six months. Likewise, either BMI calculation or waist circumference measurement should be undertaken to assess patients for comorbid conditions (e.g., MetS).

*5.4.3 **Laboratory testing***

Patients should undergo a fasting blood glucose or haemoglobin A1c and lipid profile measurement if they have not been assessed in the previous twelve months. Hormonal tests should include early morning total testosterone in a fasting state. The bio-available or calculated fT values may sometimes be needed to corroborate total testosterone measurements (see sections 3.2.1 and 3.4.1). Additional laboratory tests may be considered in selected patients with specific signs and associated symptoms (e.g., total PSA) [313], PRL and LH [314]). Although physical examination and laboratory evaluation of most men with ED may not reveal the exact diagnosis, clinical and biochemical evaluation presents an opportunity to identify comorbid conditions [312].

Figure 2: Minimal diagnostic evaluation (basic work-up) in patients with ED

ED = erectile dysfunction; IIEF = International Index of Erectile Function.



ED = erectile dysfunction; IIEF = International Index of Erectile Function.

5.4.4 Cardiovascular system and sexual activity: the patient at risk

Patients who seek treatment for sexual dysfunction have a high prevalence of CVDs. Overall, ED can improve the sensitivity of screening for asymptomatic CVD in men with diabetes [315, 316]. Erectile dysfunction significantly increases the risk of CVD, coronary heart disease, stroke and atrial fibrillation [317]. Longitudinal data from an observational population-based study of 965 men without CVD showed that younger men (especially those < 50 years) with transient and persistent ED have an increased Framingham CVD risk [318].

The current EAU Guidelines on the diagnosis and treatment of men with ED have been adapted from the recommendations from the Princeton Consensus conferences on sexual dysfunction and cardiac risk published in 2012 [319]. Over time, the Princeton Consensus (Expert Panel) Conference is dedicated to optimising sexual function and preserving cardiovascular health [319-322]. Accordingly, patients with ED have been stratified into three cardiovascular risk categories (Table 8), which can still be used as the basis for a treatment algorithm for initiating or resuming sexual activity (Figure 3): low-risk patients do not need cardiac testing or evaluation before initiation or resumption of sexual activity or therapy for sexual dysfunction; intermediate risk patients, according to the results of testing, may be moved to either the high- or low-risk group; 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.

Table 8: Cardiac risk stratification (based on 2nd and 3rd Princeton Consensus) [319, 322]

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 3: Treatment algorithm for determining level of sexual activity according to cardiac risk in ED (based on 3rd Princeton Consensus) [319]

[a] *Sexual activity is equivalent to walking 1 mile on the flat in 20 minutes or briskly climbing two flights of stairs in 10 seconds.*

[b] *Sexual activity is equivalent to 4 minutes of the Bruce treadmill protocol.*

5.5 Diagnostic Evaluation (advanced work-up)

Most patients with ED can be managed based on their medical and sexual history; conversely, some patients may need specific diagnostic tests (Table 9).

*5.5.1 **Nocturnal penile tumescence and rigidity test***

The nocturnal penile tumescence and rigidity (NPTR) test applies nocturnal monitoring devices that measure the number of erectile episodes, tumescence (circumference change by strain gauges), maximal penile rigidity, and duration of nocturnal erections. The NPTR 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 minutes [323]. Nocturnal penile tumescence and rigidity monitoring is an approach for objectively differentiating between organic and psychogenic ED (patients with psychogenic ED usually have normal findings in the NPTR test). However, many potential confounding factors (e.g., situational) may limit its routine use for diagnostic purposes [324].

*5.5.2 **Intracavernous injection test***

The intracavernous injection test gives limited information about vascular status. A positive test is a rigid erectile response (unable to bend the penis) that appears within 10 minutes after the intracavernous injection and lasts for 30 minutes [325]. Overall, the test *per se* is inconclusive as a diagnostic procedure and a duplex Doppler study of the penis should be requested, if clinically warranted.

*5.5.3 **Dynamic duplex ultrasound of the penis***

Dynamic duplex ultrasound (US) of the penis is a second-level diagnostic test that specifically studies the haemodynamic pathophysiology of EF. Therefore, in clinical practice, it is usually applied in those conditions in which a potential vasculogenic aetiology of ED (e.g., diabetes mellitus, multiple concomitant CV risk factors and/or overt peripheral vascular disease, renal transplantation and poor responders to oral therapy) is suspected. Peak systolic blood flow > 30 cm/s, end-diastolic velocity < 3 cm/s and resistance index > 0.8 are considered normal [326, 327]. Recent data suggest that duplex scanning as a haemodynamic study may be better at tailoring therapy for ED, such as for low-intensity shock wave treatment (Li-SWT) in men with vasculogenic ED [328]. Further vascular investigation is unnecessary if a duplex US examination is normal.

*5.5.4 **Arteriography and dynamic infusion cavernosometry or cavernosography***

Pudendal arteriography should be performed only in patients who are being considered for penile revascularisation [329]. At present, dynamic infusion cavernosometry or cavernosography are rarely employed as diagnostic methods for evaluating venogenic ED, and there has been concern surrounding the concept of venogenic ED.

*5.5.5 **Psychopathological and psychosocial assessment***

Mental health issues and psychological distress are frequently comorbid with ED [330]. This is most evident for depression and anxiety-related disorders, but may also include transitory states of altered mood (i.e., dysfunctional affective states resulting from a specific life stressor or crisis) [264, 331, 332]. Relationship factors, including lack of satisfaction with the partner, poor sexual relationships, length of the relationship, or feeling emotionally disconnected from the partner during sex, have been related to erectile difficulties and dysfunction [331, 333, 334]. In contrast, intimacy was found to be a protective factor in ED [253, 335]. Additionally, the cognitive factors underpinning organic and non-organic ED (i.e., all dysfunctional thinking styles and expectations about sexuality, poor self-esteem and cognitive distraction from erotic cues) must also be assessed.

Psychosexual assessment in ED cases includes a clinical interview considering all the previous topics [336]. Also, self-reported measures are frequently used within the psychosocial context [337]. A growing amount of data suggests that men who have sex with men (MSM) present specific psychological risks associated with erectile capability regarding anal sex [338]. Therefore, professionals must tailor their assessment in the context of sexual minorities.

Figure 4: Psychopathological and psychosocial assessment

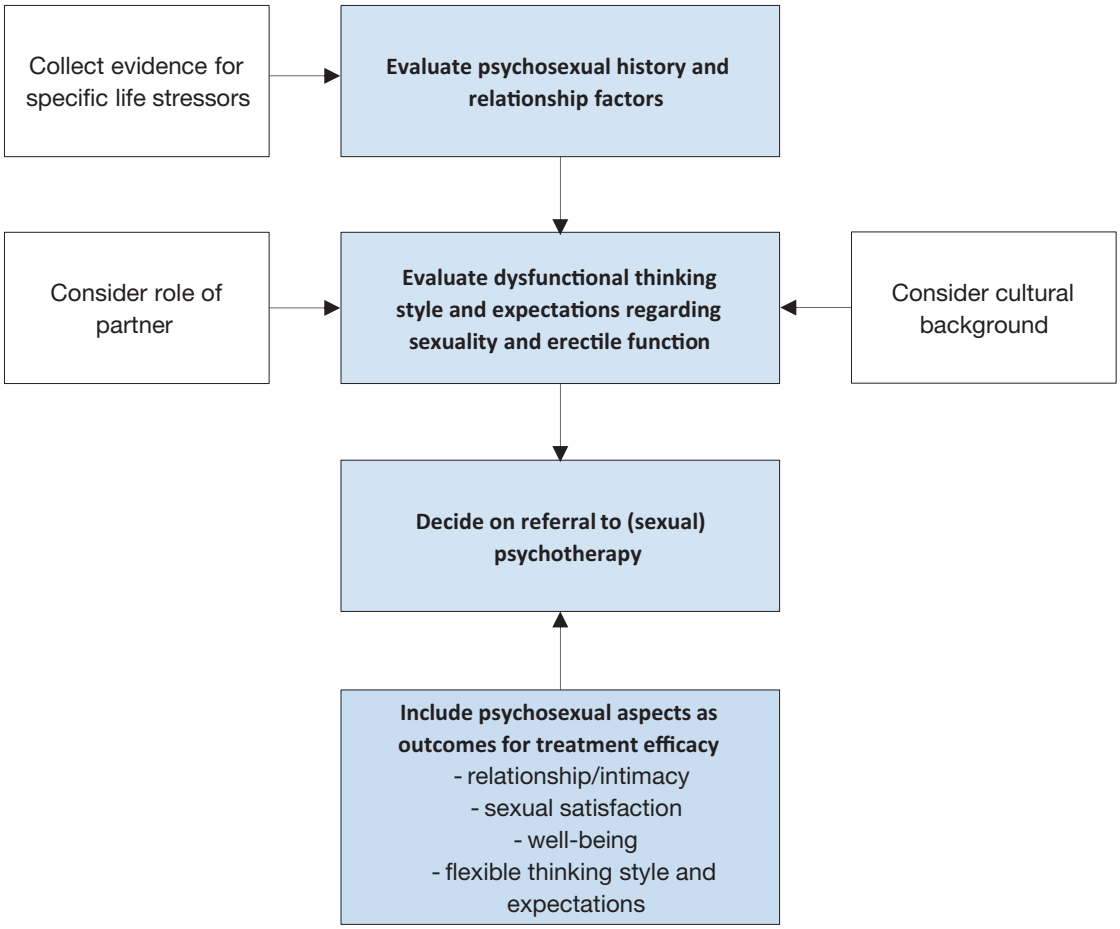


Table 9: Indications for specific diagnostic tests for ED and the specific diagnostic tests

Indications for specific diagnostic tests for ED
Primary ED (not caused by acquired organic disease or psychogenic disorder).
Young patients with a history of pelvic or perineal trauma, who could benefit from potentially curative revascularisation surgery or angioplasty.
Patients with penile deformities that might require surgical correction (e.g., Peyronie's disease and congenital penile curvature).
Patients with complex psychiatric or psychosexual disorders.
Patients with complex endocrine disorders.
Specific tests may be indicated at the request of the patient or their partner.
Medico-legal reasons (e.g., implantation of penile prosthesis to document end-stage ED, and sexual abuse).
Specific diagnostic tests for ED
Nocturnal Penile Tumescence and Rigidity (NTPR) using Rigiscan®
Vascular studies • Intracavernous vasoactive drug injection • Penile dynamic duplex ultrasonography • Penile dynamic infusion cavernosometry and cavernosography • Internal pudendal arteriography
Specialised endocrinological studies
Specialised psycho-diagnostic evaluation

5.5.6 Summary of evidence and recommendations for diagnostic evaluation of ED

Summary of evidence	LE
Medical and sexual history, physical examination and laboratory testing including metabolic and hormonal profile may identify risk factors for ED and may help in defining the ED aetiology.	3
Validated psychometric questionnaires (e.g. IIEF; EHS) are reliable tools to assess ED severity.	3
Specific diagnostic tests could be of help in discerning between vasculogenic, hormonal or psychogenic causes of ED	3

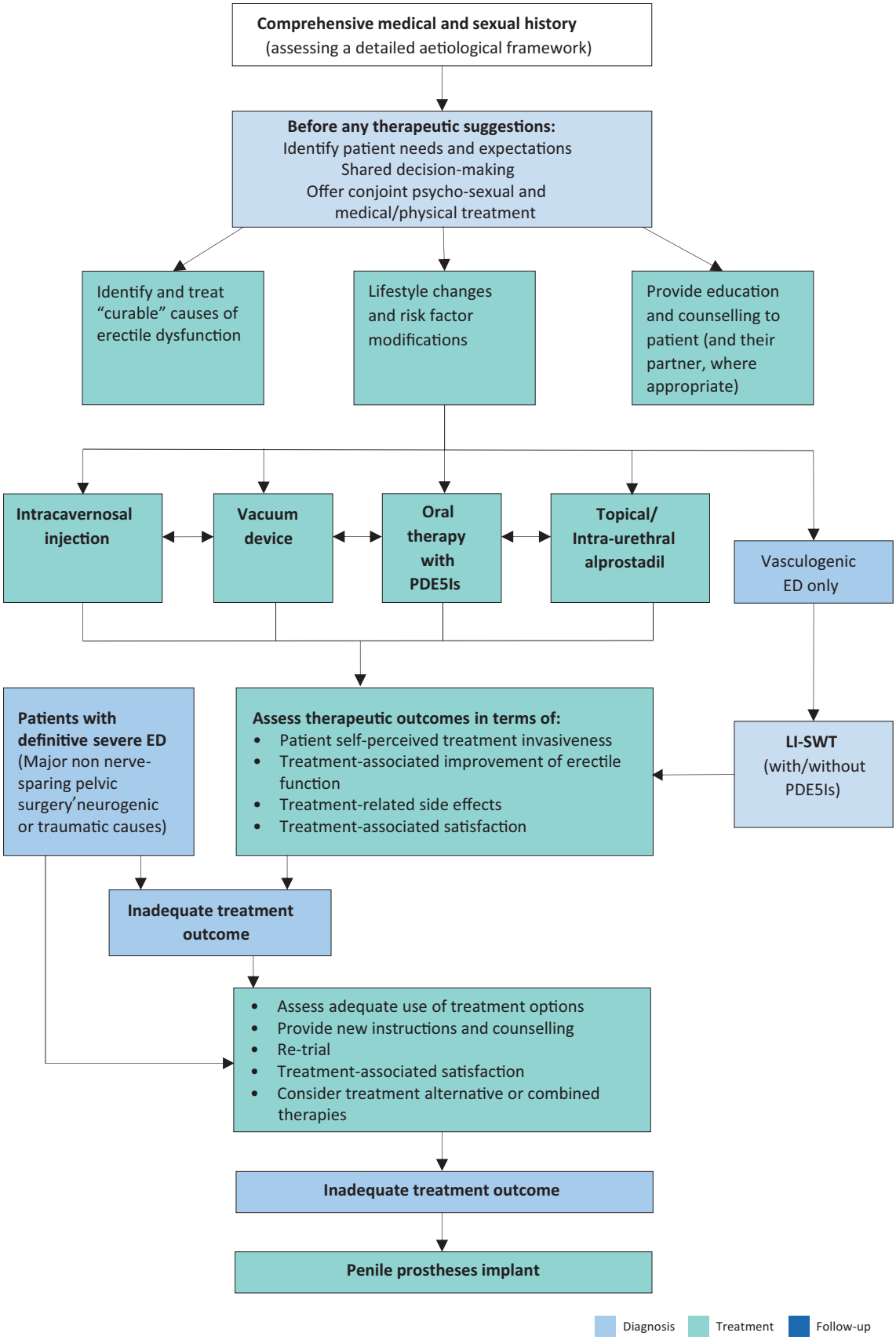
Recommendations	Strength rating
Take a comprehensive medical and sexual history in every patient presenting with erectile dysfunction (ED). Take a targeted psychosexual history, including life stressors, cultural aspects, and cognitive factors regarding patient sexual performance.	Strong
Use a validated questionnaire related to ED to assess all sexual function domains (e.g., International Index of Erectile Function) and the effect of a specific treatment modality.	Strong
Include a focused physical examination in the initial assessment of men with ED to identify underlying medical conditions and comorbid genital disorders that may be associated with ED.	Strong
Evaluate laboratory tests, including glucose and lipid profile and total testosterone, to identify and treat any reversible risk factors and lifestyle factors that can be modified.	Strong
Include specific diagnostic tests in the initial evaluation of ED in the presence of the conditions presented in Table 9.	Strong

5.6 Treatment of erectile dysfunction

The Guidelines Panel have developed a comprehensive therapeutic and decision-making algorithm (Figure 5) for treating ED. The treatment algorithm was developed as an alternative to the traditional three-tier concept, to support personalised treatment tailored to individual patients, according to the invasiveness, tolerability and effectiveness of the different therapeutic options and patients' expectations. In this context, patients should be fully counselled with respect to all available treatment modalities.

The majority of men with ED are not treated with cause-specific therapeutic options. This results in a tailored treatment strategy that depends on invasiveness, efficacy, safety and costs, as well as patient preference [339]; therefore, physician-patient dialogue is essential throughout the management of ED. A systematic review has shown a consistent discontinuation rate for all available ED treatment options. This highlights the importance of clinicians understanding patient's beliefs about ED treatment, therapeutic ineffectiveness, adverse effects, quality of intimate relationships and treatment costs all of which were shown to be the most prevalent barriers to treatment use [340].

Figure 5: Management algorithm for erectile dysfunction



ED = erectile dysfunction; PDE5Is = phosphodiesterase type 5 inhibitors; Li-SWT = low-intensity shockwave therapy.

*5.6.1 **Patient education***

Educational intervention is often the first approach to sexual complaints, and consists of informing patients about the psychological and physiological processes involved in the individual's sexual response, in ways the patient can understand. This baseline approach has been shown to favour sexual satisfaction in men with ED [341]. Accordingly, consultation with the patient should include a discussion of the expectations and needs of the patient's and his sexual partner. It should also review the patient's and partner's understanding of ED and the results of diagnostic tests, and provide a rationale for treatment selection [339].

*5.6.2 **Modifiable risk factors***

Erectile dysfunction may be associated with modifiable or reversible risk factors, including lifestyle or drug-related factors [342]. 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 (e.g., endocrine disorders and metabolic disorders such as diabetes, and some cardiovascular problems such as hypertension) which should always be well-controlled as the first step of any ED treatment [343]. Overall, several studies have shown that lifestyle modifications including physical activity, weight loss and treatment for CVD risk factors and lipid-lowering therapy with statins may be of help in improving sexual function in men with ED [257, 342, 344-349].

*5.6.3 **Phosphodiesterase type 5 inhibitors***

Four potent selective PDE5Is have been approved by the EMA for the treatment of ED [350]. The efficacy of all four PD5EIs in almost every subgroup of patients with ED has been successfully established [350-353]. Efficacy is defined as an erection, with rigidity, sufficient for satisfactory intercourse [343]. In addition, adverse events for the four PDE5Is are generally mild and self-limiting [354-358]. The pharmacokinetic data for all four PDE5Is and their associated adverse events are presented in Tables 10 and 11, respectively. The choice of PDE5I depends on the frequency of intercourse and the patient's personal experience. Two meta-analyses demonstrated that ED patients who prioritise high efficacy should use sildenafil 50 mg whereas those who optimise tolerability should initially use tadalafil 10 mg [351, 359].

5.6.3.1 Sildenafil

Sildenafil 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 adverse effects [360]. The window of effectiveness ranges from 30-60 minutes after administration [360] up to 12 hours [361]. In a 24-week dose-response study, improved erections were reported by 56%, 77% and 84% of general ED patients taking 25, 50 and 100 mg sildenafil, respectively, compared to 25% of men taking placebo [362]. Sildenafil also significantly improved patient scores for IIEF, sexual encounter profile question 2 (SEP2), SEP question 3 (SEP3), General Assessment Questionnaire (GAQ) and treatment satisfaction [362]. Furthermore, an orally disintegrating tablet (ODT) of sildenafil citrate at a dose of 50 mg has been developed, mainly for patients who have difficulty swallowing solid dosage forms.

5.6.3.2 Tadalafil

Tadalafil is administered in on-demand doses of 10 and 20 mg or a 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 adverse effects [363, 364]. The window of effectiveness ranges from 30 minutes after administration (peak efficacy after approximately 2 hours) up to 36 hours [363]. In a twelve-week dose-response study, improved erections were reported by 67% and 81% of men with ED taking 10 and 20 mg tadalafil, respectively, compared to 35% of men taking placebo [363]. Tadalafil has also been shown to have a net clinical benefit in the short-term on ejaculatory and orgasmic functions in ED patients [365].

Data have also shown that 40% of men aged > 45 years were combined responders for ED and LUTS/BPH when treated with tadalafil 5 mg once daily, with symptom improvement after twelve weeks [366]. Therefore, its use may be considered in both patients with ED only and in patients also complaining of concomitant LUTS, and wishing to benefit from a single therapy [367].

5.6.3.3 Vardenafil

Vardenafil is administered in on-demand doses of 5, 10 and 20 mg. The recommended starting dose is 10 mg and should be adapted according to the patient's response and adverse effects [356]. Vardenafil is effective from 30 minutes after administration [368], with one of three patients achieving satisfactory erections within 15 minutes of ingestion [369]. In a twelve-week dose-response study, improved erections were reported by 66%, 76% and 80% of men with ED taking 5, 10 and 20 mg vardenafil, respectively, compared with 30% of men taking placebo [356, 370]. Vardenafil significantly improved patient scores for IIEF, SEP2, SEP3, and GAQ and treatment satisfaction. An orodispersable tablet (ODT) formulation of vardenafil has also been released [370]. The efficacy of vardenafil ODT has been demonstrated in several RCTs and did not seem to differ from the regular formulation [371-373].

5.6.3.4 Avanafil

Avanafil is administered in on-demand doses of 50, 100 and 200 mg [357]. The recommended starting dose is 100 mg taken as needed 15-30 minutes before sexual activity and the dose may be adapted according to efficacy and tolerability [357, 358, 374]. In a general ED population the mean percentage of successful sexual attempts resulting in intercourse were 47%, 58% and 59% for the 50, 100 and 200 mg groups, respectively, as compared with 28% for the placebo group [357, 358]. A meta-analysis confirmed that avanafil had comparable efficacy with sildenafil, vardenafil and tadalafil [375].

5.6.3.5 Continuous use of PDE5Is

According to the EMA, a once-daily regimen with tadalafil 2.5 or 5 mg may be considered suitable, based on patients' choice and physicians' judgement. In these patients, the recommended dose is 5 mg, taken once daily at approximately the same time each day. Tadalafil, 5 mg once daily, provides an alternative to on-demand 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 linked. Regardless of the type of ED population, there is no clinically significant difference between a tadalafil treatment administered once daily vs. on-demand tadalafil [376]. Overall, treatment with tadalafil 5 mg once daily in men complaining of ED of various severities is well-tolerated and effective [377] and may improve EF among men who have a partial response to on-demand PDE5I therapy [378]. The appropriateness of the continuous use of a daily regimen should be re-assessed periodically [377, 379].

Table 10: Pharmacokinetics data for PDE5Is EMA approved for the treatment of ED*

Parameter	Sildenafil, 100 mg	Tadalafil, 20 mg	Vardenafil, 20 mg	Avanafil, 200mg
C_{max}	560 µg/L	378 µg/L	18.7 µg/L	5.2 µg/L
T_{max} (median)	0.8-1 hours	2 hours	0.9 hours	0.5-0.75 hours
T1/2	2.6-3.7 hours	17.5 hours	3.9 hours	6-17 hours
AUC	1,685 µg.h/L	8,066 µg.h/L	56.8 µg.h/L	11.6 µg.h/L
Protein binding	96%	94%	94%	99%
Bioavailability	41%	NA	15%	8-10%

** Fasted state, higher recommended dose. Data adapted from EMA statements on product characteristics.*
C_{max} = maximal concentration; T_{max} = time-to-maximum plasma concentration; T1/2 = plasma elimination halftime; AUC = area under curve or serum concentration-time curve.

Table 11: Common adverse events of the four PDE5Is currently EMA-approved to treat ED*

Adverse event	Sildenafil	Tadalafil	Vardenafil	Avanafil, 200mg
Headache	12.8%	14.5%	16%	9.3%
Flushing	10.4%	4.1%	12%	3.7%
Dyspepsia	4.6%	12.3%	4%	uncommon
Nasal congestion	1.1%	4.3%	10%	1.9%
Dizziness	1.2%	2.3%	2%	0.6%
Abnormal vision	1.9%		< 2%	None
Back pain		6.5%		< 2%
Myalgia		5.7%		< 2%

** Adapted from EMA statements on product characteristics.*

5.6.3.6 Safety concerns for PDE5Is

5.6.3.6.1 Cardiovascular safety

No RCTs or open-label studies have demonstrated an increase in myocardial infarction rates in patients receiving PDE5Is. None of the PDE5Is have an adverse effect on total exercise time or time-to-ischaemia during exercise testing in men with stable angina [350, 380]. This EAU Guidelines panel agrees to maintain the recommendations provided by the 3rd Princeton Consensus Panel in terms of the prescription of all PDE5Is in patients with CVD or in those with high CV risk [319, 321, 322].

5.6.3.6.2 Contraindications for the concomitant use of organic nitrates and nicorandil

An absolute contraindication to PDE5Is is the concomitant use of any form of organic nitrate or NO donors including recreational use of amyl nitrite or nitrate (poppers). Concomitant use results in cGMP accumulation unpredictable falls in blood pressure and symptoms of hypotension [381-384]. Concurrent use of nicorandil and PDE5Is is contraindicated due to the potential of the nitric oxide donating properties of nicorandil to increase cGMP levels [385].

5.6.3.6.3 Antihypertensive drugs

Co-administration of PDE5Is with antihypertensive agents may result in small additive decreases in blood pressure, which are usually minor [319]. 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 [386].

5.6.3.6.4 Interactions with α-blockers

Tadalafil 5 mg is currently the only licensed drug for the treatment of both ED and LUTS demonstrating overall good efficacy in relieving urinary symptoms and improving EF [367]. Therefore, treatment with tadalafil 5 mg should be considered in patients suffering from mild to moderate LUTS associated with ED either alone or in combination with α-blockers. Conversely, as both drugs are vasodilators a certain degree of caution has been observed for combination therapy with PDE5Is and alpha-blockers due to the potential cumulative effects on blood pressure described in some studies [361, 369, 387]. However, a meta-analysis concluded that a concomitant treatment with α-blockers [both non-uroselective (e.g., terazosin and doxazosin) and uro-selective (e.g., alfuzosin, tamsulosin and silodosin] and PDE5Is may produce changes in haemodynamic parameters, but it does not increase the rate of adverse events due to hypotension [387]. Therefore, there is no current limitation in the simultaneous use of α-blockers and PDE5I.

5.6.3.7 Management of non- or poor-responders to PDE5Is

The management of non-responders depends upon identifying the underlying cause [388].

Clinicians should begin by ensuring that the medication has been properly prescribed, is being correctly used by the patient and that the patient has been using a licensed medication. Absorption of sildenafil, vardenafil and avanafil can be delayed by high-fat meals [389-391]. Timing is important and patients may be waiting either too short or too long after the medication before attempting sexual intercourse. Studies suggest that patient education can help salvage an apparent non-responder to a PDE5I [388, 392-395]. After emphasising the importance of dose, timing, and sexual stimulation to the patient, EF can be effectively restored following re-administration of the relevant PDE5I [388, 392, 393].

Studies have demonstrated that hypogonadal patients not responding to PDE5Is may improve their response to PDE5Is after initiating testosterone therapy [85, 343, 396]. Therefore, if diagnostic criteria suggestive of testosterone deficiency are present, testosterone therapy may be more appropriate even in ED patients [3, 85].

Limited data suggest that some patients might respond better to one PDE5I than to another [397], raising the possibility that, despite an identical mode of action, switching to a different PDE5I may be beneficial. However, no evidence for this has been reported in the available RCTs [398, 399].

In refractory, complex, or difficult-to-treat cases of ED combination therapy should be considered as a first-line approach. Although the available data are still limited, combining PDE5I with antioxidant agents, Li-SWT or a vacuum erection device (VED) improves efficacy outcomes, without any significant increase in adverse events [400]. Similarly, the association of daily tadalafil with a short-acting PDE5I (such as sildenafil) leads to improved outcomes, without any significant increase in adverse effects [401].

5.6.3.8 Topical/Intraurethral alprostadil

The vasoactive agent alprostadil can be administered inside the urethra in two different formulations. The first delivery method is topical, using a cream that includes a permeation enhancer to facilitate the absorption of alprostadil (200 and 300 µg) via the urethral meatus [402, 403]. Clinical data are still limited. Significant improvement compared to placebo was recorded for IIEF-EF domain score, SEP2 and SEP3 in a broad range of patients with mild-to-severe ED [404]. Adverse effects include penile erythema, penile burning, and pain that usually resolve within two hours of application. Topical alprostadil (VITAROSTM) at a dose of 300 µg is available in some European countries. Recently, a randomised cross-over clinical trial has shown that, compared to the standard administration route, direct delivery within the urethral meatus can increase efficacy and confidence among patients, without increasing adverse effects [405].

The second delivery method is by intra-urethral insertion of a specific formulation of alprostadil (125-1000 µg) in a medicated pellet (MUSE™) [229]. Erections sufficient for intercourse are achieved in 30-65.9% of patients. In clinical practice, it is recommended that intra-urethral alprostadil is initiated at a dose of 500 µg, as it has a higher efficacy than the 250 µg dose, with minimal differences with regards to adverse events. In case of unsatisfactory clinical response, the dose can be increased to 1000 µg [406-408]. Overall, the most common adverse events are local pain (29-41%) and dizziness with possible hypotension (1.9-14%). Penile fibrosis and priapism are 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 for intracavernous pharmacotherapy [409], with 30% adherence to long-term therapy. Intraurethral pharmacotherapy provides an alternative to intracavernous injections in patients who prefer a less-invasive, although less-efficacious treatment.

*5.6.4 **Psychosocial intervention and therapy***

Psychosocial interventions including different modalities (e.g., sexual skills training, marital therapy, psychosexual education) [341], and Cognitive and Behavioural Therapy (CBT - group or couple format), are recommended [336]. Cognitive and Behaviour Therapy is aimed at altering dysfunctional cognitive and behavioural patterns influencing ED, and increasing adjustment during the course of the disorder. The CBT approach combined with medical treatment for ED has received empirical support and is considered an optimal procedure [410].

*5.6.5 **Hormonal treatment***

When clinically indicated, testosterone therapy (intramuscular, transdermal, or oral) can be considered for men with low or low-normal testosterone levels and concomitant problems with their sexual desire, EF and dissatisfaction derived from intercourse and overall sex life (see Section 3.4 for a comprehensive discussion of testosterone therapy) [411].

*5.6.6 **Vacuum erection devices***

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% [412, 413]. Long-term use of VEDs decreases to 50-64% after two years [414]. The most common adverse events include pain, inability to ejaculate, petechiae, bruising, and numbness [413]. Serious adverse events (skin necrosis) can be avoided if patients remove the constriction ring within 30 minutes. Vacuum erection devices are contraindicated in patients with bleeding disorders or on anticoagulant therapy [415, 416]. Vacuum erection devices may be the treatment of choice in well-informed older patients with infrequent sexual intercourse and comorbidity requiring non-invasive, drug-free management of ED [412, 413, 417].

*5.6.7 **Intracavernous injections therapy***

Intracavernous administration of vasoactive drugs was the first medical treatment introduced for ED [395, 418]. Patients may be offered intracavernous injections at every stage of a tailored treatment work-up.

5.6.7.1 Alprostadil

Alprostadil (Caverject™, Edex/Viridal™) was the first and only drug approved for intracavernous treatment of ED [395, 419]. Intracavernous alprostadil is most efficacious as a monotherapy at a dose of 5-40 µg (40 µg may be offered off-label in some European countries). The erection appears after 5-15 minutes and lasts according to the dose injected, but with significant heterogeneity among patients. An office-training programme is required for patients to learn the injection technique. Efficacy rates for intracavernous alprostadil of > 70% have been found in the general ED population, as well as in patient subgroups (e.g., men with diabetes or CVD), with reported satisfaction rates of 87-93.5% in patients and 86-90.3% in partners after the injections [395, 418]. Complications of intracavernous alprostadil include penile pain (50% of patients reported pain only after 11% of total injections), excessively prolonged and undesired erections (5%), priapism (1%), and fibrosis (2%) [395, 418, 420]. Pain is usually self-limited after prolonged use and it can be alleviated with the addition of sodium bicarbonate or local anaesthesia [395, 418, 421]. Cavernosal fibrosis 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 the need to discontinue intracavernous injections indefinitely. Systemic adverse 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 reported for intracavernous pharmacotherapy [395, 418, 422, 423], with most discontinuations occurring within the first two to three months. Careful counselling of patients during the office-training phase as well as close follow-up are important in addressing patient withdrawal from an intracavernous injection programme [424-426].

5.6.7.2 Other vasoactive intracavernous treatments

Table 12 details the available intracavernous injection therapies (compounds and characteristics). Combination therapy enables a patient to take advantage of the different modes of action of the drugs being used, as well as alleviating adverse 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 because of its high incidence of adverse 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. Phentolamine is currently not licensed for the treatment of ED.
- Limited data 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 [427, 428]. Most combinations are not standardised and some drugs have limited availability worldwide.
- Bimix, (papaverine 7.5-45 mg plus phentolamine 0.25-1.5 mg) and Trimix (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 [429, 430]. Trimix has the highest efficacy rates, reaching 92%; this combination has similar adverse 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 the total dose).
- Invicorp™: Vasoactive intestinal peptide (25 µg) plus phentolamine mesylate (1-2 mg Invicorp), is a combination of two active components with complementary modes of action. Clinical studies have shown that the combination is effective 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 low incidence of penile pain and a virtually negligible risk of priapism [431].

Overall, despite high efficacy rates, 5-10% of patients do not respond to combination therapy with intracavernous injections.

Table 12: Intracavernous injection therapy - compounds and characteristics

Name	Substance	Dosage	Efficacy	Adverse Events	Comment
Caverject™ or Edex/Viridal™	Alprostadil	5-40 µg/mL	~ 70%	Penile pain, priapism, fibrosis	Easily available
Papaverine	Papaverine	20 - 80 mg	< 55%	Elevation of liver enzymes, priapism, fibrosis	Abandoned as monotherapy
Phentolamine	Phentolamine	0.5 mg/mL	Poor efficacy as monotherapy	Systemic hypotension, reflex tachycardia, nasal congestion, and gastrointestinal upset	Abandoned as monotherapy
Bimix	Papaverine + Phentolamine	30 mg/mL + 0.5 mg/mL	~ 90%	Similar to Alprostadil (less pain)	Not licensed for the treatment of ED
Trimix	Papaverine + Phentolamine + Alprostadil	30 mg/mL + 1 mg/mL + 10 µg/mL	~ 92%	Similar as Alprostadil (less pain)	Not licensed for the treatment of ED
Invicorp™	Vasoactive intestinal peptide (VIP) + Phentolamine	25 µg + 1-2 mg	~ 80%	Similar to Alprostadil without pain	Easily available

5.6.8 ***Innovative treatment modalities***

There are currently several potential novel treatment modalities for ED. Most of these therapeutic approaches require further investigation in large-scale, blinded, placebo-controlled randomised studies to achieve adequate evidence-based and clinically-reliable recommendation grades [432-437].

5.6.8.1 Regenerative medicine therapies

5.6.8.1.1 Shockwave therapy

The use of low-intensity extracorporeal shock wave therapy (Li-SWT) has been increasingly proposed as a treatment for vasculogenic ED over the last decade, and it's the only currently marketed treatment that might offer a cure, which is the most desired outcome for most men suffering from ED [328, 438-445].

Overall, several single-arm trials have shown a beneficial effect of Li-SWT on patient-reported EF, but data from prospective randomised trials are conflicting, and many questions remain to be answered due to the heterogeneity among shockwave generators, type of shockwaves delivered, set-up parameters and treatment protocols [446, 447]. In a trial trying to assess the best treatment parameters, no significant differences were observed between various energy flux density levels; although, a 0.10 mJ/mm^2 seems to perform slightly better than lower energies [448]. Most of the studies have suggested that Li-SWT can significantly increase IIEF and EHS scores in patients with mild vasculogenic ED, although this improvement appears modest and the rates of patients reporting a satisfactory improvement range between 40-80% [328, 446]. Few studies have shown an improvement in penile haemodynamic parameters after Li-SWT, but the clinical meaning of this improvement remains unclear [446, 449]. Likewise, data suggest that Li-SWT could ameliorate erection quality even in patients with severe ED who are either PDE5Is non-responders [443, 450, 451] or inadequate responders [452], thus reducing the immediate need for more invasive treatments. Treatment effect appears to be clinically evident starting from one to three months after treatment completion, with a subsequent progressive decrease of the achieved benefit in terms of EF over time, although some effects could be still detected up to five years after treatment [446, 448, 453]. Data from RCTs suggests that even better results could be achieved by combining Li-SWT with other treatments such as a VED in men with T2DM [454] or daily tadalafil [455, 456].

Findings from a recent meta-analysis showed that LI-ESWT has a positive effect on early recovery of EF in the context of penile rehabilitation of ED after RP. However, the authors clearly outlined that the level of evidence was low; therefore, careful interpretation of the results is required [457-459].

5.6.8.1.2 Platelet-Rich Plasma

Intracavernous injection of platelet-rich plasma (PRP) has been investigated in several prospective and retrospective trials [460-466]. The regenerative effect of PRP is deemed to be exerted through the high concentrations of platelets containing several growth factors including VEGF, EGF, IGF-1, PDGF and FGF [467]. These factors may be responsible for angiogenesis stimulation and stem cell recruitment [467].

In the first RCT investigated the effect of intracavernous injection of PRP for ED, 60 patients with mild to moderate vasculogenic ED were randomised to receive two injections of 10 mL PRP (n=30) or placebo (n=30) [466]. At one, three and six-month follow-up, the rate of patients reporting minimal clinically important difference (MCID) in the IIEF-EF score was significantly higher in the treatment group, with 69% achieving MCID six months after PRP vs. 27% in the placebo group ($p < 0.001$). IIEF-EF scores improved by a mean of 2.7 points at one-month and 3.9 points at six-month assessment after treatment. Regarding safety, no haemorrhagic events or other side effects were reported [466].

A prospective randomized, double-blind, placebo-controlled study was carried out on 109 patients, aged 45-65 years, with mild to moderate ED, following cessation of any ED treatment [468]. At one, three and six months after PRP injections, patients in the PRP group had a significant improvement compared to placebo in terms of IIEF-EF, SEP2 and SEP3. Moreover, at six months post-treatment follow-up, 70% of patients achieved an MCID in the PRP group compared to 16% in the placebo group [468]. Even more recently, a further prospective, randomized, double-blind, placebo-control study on a relatively small cohort of mild to moderate ED patients who have been treated with two PRP injections separated by one month showed that the treatment is safe, but the authors did not find any difference in efficacy between PRP and placebo [469]. Of clinical relevance, patients were allowed to keep PDE5is during the study [469].

As a whole, despite a number of promising results that have been obtained for the treatment of primary organic ED in terms of both efficacy and safety of PRP, the available evidence is still insufficient to provide a recommendation regarding the use of PRP for ED treatment in clinical practice [470]. In this context, an important heterogeneity among studies still exists in terms of timing and dosing regimens, with no consensus regarding the optimal activation method and platelet concentration for each PRP injection, and the need to measure qualitative and quantitative composition of growth factors and cytokines [470, 471]. Therefore, intracavernous injection of PRP should be used only in a clinical trial setting, as larger trials are needed to confirm original findings and define the efficacy and safety of PRP for ED.

5.6.8.1.3 Stem-cells

The use of stem cells as a regenerative treatment for ED is currently under investigation. A systematic review has concluded that five completed human clinical trials have shown promise for stem cell therapy as a restorative treatment for ED [472]. However, data are still insufficient for providing a clinical recommendation.

5.6.8.2 Botulinum Neurotoxin

Botulinum Neurotoxin A (BoNT-A) has been investigated as a possible ED treatment [473]. Two RCTs have investigated the effect of BoNT-A for the treatment of patients with ED who were non-responders to PDE5Is or ICI pro-erectile drugs [474, 475]. One trial randomised 70 patients with ED refractory to PDE5Is to receive a single ICI of 100 UI of BoNT-A or saline [474]. Patients in both groups were instructed to keep using on-demand high-dose PDE5Is. The RCT showed an improvement in EHS and PSV at two weeks post-treatment. At six weeks the treatment group showed a 5 points improvement in the SHIM score vs. no improvement in the placebo group, with 53% of patients reporting an erection hard enough for vaginal penetration [474]. The second trial randomised 176 patients, all non-responders to PDE5Is or ICI trimix, to three treatment groups: BoNT-A 100 UI; BoNT-A 50 UI; or placebo [475]. A significant improvement in SHIM, EHS and SEP scores was reported in both treatment groups with a maximum response rate being reacted three months after treatment. Overall, the RCT showed that up to 40% of patients were able to resume satisfactory sexual activity after treatment [475]. Both trials reported only mild local side-effects with no systemic complications.

Other single-arm, non-controlled studies have confirmed these findings [476, 477]; therefore, showing a promising role for BoNT-A in the treatment of patients who are non-responders to well-established ED therapies. However, at present no recommendation for its use in clinical practice can be provided as larger trials are needed to confirm original findings and define the efficacy and safety of BoNT-A for ED.

5.6.9 ***Herbal medicine and natural supplements***

In recent years there has been an exponential growth in the market of medicinal herbs and natural supplements for the treatment of ED, but with very little available evidence of robust scientific data to support their efficacy and safety. A Cochrane review showed that ginseng may only have trivial effects on erectile function or satisfaction with intercourse compared to placebo when assessed using validated tools [478]. Moreover, data suggested that daily administration of oral L-arginine, only when in combination with PDE5I use, improves sexual function [479].

5.6.10 ***Erectile dysfunction after radical prostatectomy***

The use of pro-erectile drugs following RP is important in achieving post-operative EF and allowing patients to resume sexual activity. Several trials have shown improvements in EF after RP in patients receiving drugs (any therapeutic or prophylactic) for ED. Early compared with delayed EF treatment affects the natural recovery time for EF [480], although there is limited data to support any specific regimen, which is either optimal for penile rehabilitation or may result in the achievement of spontaneous, non-pharmacologically assisted erections [289, 481, 482]. In prospective studies, there is no evidence that penile rehabilitation itself increases the chances of spontaneous recovery of EF in men following nerve-sparing RP (NSRP) [482]. The currently available therapeutic armamentarium follows the treatment algorithm for ED, which is shown in Figure 3.

In this context, PDE5Is have been considered as the first-line therapy in patients who have undergone NS surgery, regardless of the surgical technique used [289, 293]. Several clinical parameters have been identified as potential predictors of PDE5Is outcomes in men undergoing RP, i.e., patient age, baseline EF, and quality of NS technique are key factors in preserving post-RP EF [293, 296, 483].

A Cochrane review analysing data from eight RCTs showed that scheduled PDE5Is may have little or no effect on short-term (up to twelve months) self-reported potency when compared to placebo or no treatment [484]. In this study, a daily PDE5I made little to no difference in short- and long-term EF. The authors conclude that penile rehabilitation strategies using PDE5I following RP do not increase self-reported EF compared to on-demand use.

Intracavernous injections and penile implants have been traditionally suggested as second- and third-line treatments, respectively, when oral PDE5Is are not adequately effective or not suitable for post-operative patients [289, 485]. A meta-analysis showed that the early use of VED has an excellent therapeutic effect on post-RP patients and no serious adverse effects, therefore it should be considered as a therapeutic alternative [486]. Findings from two network meta-analyses showed that combination therapy with VED and PDE5is offers clear advantages over monotherapy, even in post-RP patients; therefore, this combined approach should be considered in the clinical management of ED after RP [487].

Findings from a systematic review suggested that pelvic floor muscle training (PFMT) combined with bio-feedback is a promising alternative to pharmacological treatments, although there is a need for future well-powered, rigorously designed RCTs to draw strong conclusions [488].

5.6.11 Surgical management

5.6.11.1 Surgery for post-traumatic arteriogenic ED

In young patients with pelvic or perineal trauma, surgical penile revascularisation has a 60-70% long-term success rate [416, 489]. The stenosis must be confirmed by penile pharmaco-arteriography. Corporeal veno-occlusive dysfunction is a contraindication to revascularisation.

5.6.11.2 Venous ligation surgery

Venous ligation surgery for veno-occlusive dysfunction is no longer recommended because of poor long-term results [489].

5.6.11.2.1 Penile prostheses

The surgical implantation of a penile prosthesis may be considered in patients who i) are not suitable for different pharmacotherapies or prefer a definitive therapy; and, ii) do not respond to other treatment modalities (Figure 5) [490].

The two currently available classes of penile implants include inflatable (two- and three-piece) and semi-rigid devices (malleable, mechanical and soft flexible) [293, 491-494]. There are currently no head to head studies comparing the different manufacturers' implants, demonstrating superiority of one implant type over another [495]. Patients may prefer the three-piece inflatable devices due to the more "natural" erections obtained, although no prospective RCTs have compared satisfaction rates with both types of implants. The two-piece inflatable prosthesis can be a viable option among patients who are deemed at high-risk of complications with reservoir placements (e.g., previous abdominal surgery). Semi-rigid prostheses result in a firm penis, which may be manually placed in an erect or flaccid state and offer the advantage of a simple implant technique, as well as easy use for the patient [293, 491-493]. Conversely, they can have the disadvantage of unnatural persistent erection and reduced concealability [493, 496]. They may also be an option in men with limited manual dexterity.

There are two main surgical approaches for penile prosthesis implantation: peno-scrotal and infrapubic [492, 493, 496, 497]. A systematic review comparing the satisfaction and complication rates of the different surgical approaches has shown that there is no specific advantage between the two, but rather it is recommended that surgeons have knowledge of both techniques and are capable of tailoring the incision strategy for complex cases [498]. 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 with appropriate counselling [293, 491, 492, 499-507]. Focused psychosexual counselling may improve sexuality and sexual well-being in both patients and their partners after penile implant surgery [508]. There is sufficient evidence to recommend this approach in patients who do not respond to less-invasive treatments due to its high efficacy, safety and satisfaction rate [509].

The two main complications of penile prosthesis implantation are mechanical failure and infection. Several technical modifications of the most commonly used three-piece prostheses (e.g., AMS 700CX/CXR™ and Titan Zero degree™) resulted in mechanical failure rates of < 5% after five years of follow-up [491, 510, 511]. Careful surgical techniques with appropriate antibiotic prophylaxis against Gram-positive and negative bacteria reduced infection rates to 2-3% with primary implantation in low-risk patients and high-volume centres [512-515]. The infection rate may be further reduced to 1-2% by implanting an antibiotic-impregnated prosthesis (AMS Inhibizone™) or hydrophilic-coated prosthesis (Coloplast Titan™) [491, 512, 516-519]. Methods that appear to decrease infection rates include using coated prosthesis and strictly adhering to surgical techniques and protocols that avoid prolonged wound exposure and minimise skin contact (i.e., no-touch technique).
Techniques that might prevent penile prostheses infection but lack definitive evidence include the use of prolonged post-operative antibiotics (> 24 hours), shaving with clippers, and preparation with chlorhexidine-alcohol [520, 521]. Identification and pre-treatment of patients who are colonised with nasal *Staphylococcus aureus* with mupirocin and chlorhexidine before surgery has been shown to reduce the incidence of post-operative surgical site infection from 4.4% to 0.9% RCT [522].

A large database-study has shown that diabetes mellitus is a risk factor for penile prostheses infection, highlighting the need for optimal patient selection [667]. Unfortunately, there are no RCTs determining the ideal and/or correct threshold of glycated haemoglobin that is acceptable prior to implant surgery in diabetic patients [523]. Also, there are no RCTs establishing the optimal or appropriate threshold of glycated haemoglobin deemed acceptable before implant surgery in diabetic patients [524]. A large-cohort, multicentre, retrospective analysis in men with diabetes who received a Coloplast Titan™ implant demonstrated that vancomycin plus gentamicin was the most efficacious combination of antibiotics used for implants dipping in terms of preventing postoperative infection and subsequent explantation and revision [525].

Prosthetic infection requires removal of the prosthesis and antibiotic administration. Alternatively, removal of the infected device with immediate salvage and replacement with a new prosthesis has been described using a wash-out protocol with successful salvages achieved in > 80% of cases [513, 526-528]. An absolute recommendation on how to proceed after explantation in this setting cannot be given and must be focused on the pros and cons of salvage therapy after full consultation with the patient.

Besides infection and mechanical failure, impending implant erosion involving the distal corpora, urethra, or glans can occur in 1-6% of cases after surgery [529]. Similarly, glans ischaemia and necrosis have been reported in about 1.5% of patients [529, 530]. Risk factors for these serious complications are higher in those patients with significant vascular impairment, such as patients with diabetes, or who have undergone concomitant lengthening procedures.

5.6.12 Summary of evidence and recommendations for treatment of ED

Summary of evidence
Lifestyle changes can lead to ED improvement in specific populations.
PDE5Is are associated with significant improvement of erectile function (EF) with a good overall safety profile.
There are no demonstrated differences among different PDE5Is in terms of treatment efficacy.
Topical/intraurethral alprostadil is effective in improving EF but data are still limited.
Vacuum therapy can improve EF with a wide range of treatment satisfaction rate.
Intracavernous injection with alprostadil is an effective treatment for ED; however, it has relatively high treatment drop-out rates.
Low-intensity shockwave therapy can a mild improvement in EF among patients with vasculogenic ED.
Intracavernous injections of PRP have led to a mild improvement of EF among patients with organic ED, but the available evidence is still insufficient to provide a recommendation regarding its use.
BoNT-A has been shown to improve response rate to medical treatment for ED in patients who were non-responsive to oral or injective therapies, but data are still limited.
Penile rehabilitation with PDE5Is after RP does not increase the chance of spontaneous EF recovery.
Penile prosthesis implantation is associated with high satisfaction rate among patients with ED.
There is no difference in terms of efficacy and safety among different penile implants available or surgical approaches used.

Recommendations	**Strength rating**
Fully inform patients of the mechanism of action and how phosphodiesterase type 5 inhibitors (PDE5Is) should be taken, as incorrect use/inadequate information is the main causes of a lack of response to PDE5Is.	Strong
Direct the patient to Cognitive Behaviour Therapy as a psychological approach (include the partner), when indicated, combined with medical treatment to maximise treatment outcomes.	Strong
Discuss with patients undergoing active treatment for prostate cancer (PCa) about the risk of sexual changes other than erectile dysfunction (ED), including sexual desire reduction, changes in orgasm, anejaculation, Peyronie like disease and penile size changes.	Strong
Initiate lifestyle changes and risk factor modification prior to, or at the same time as, initiating ED treatments.	Strong
Use PDE5Is as first-line therapy for the treatment of ED.	Strong

Use intracavernous injections as an alternative first-line therapy in well-informed patients or as second-line therapy.	Strong
Use topical/intra-urethral alprostadil as an alternative first-line therapy in well-informed patients who: • do not wish to have or are not suitable for oral vasoactive therapy; • do not wish to have intracavernous injections; • in patients who prefer a less-invasive therapy.	Weak
Use low-intensity shockwave treatment (Li-SWT) with/without PDE5Is in patients • with mild vasculogenic ED; • as an alternative therapy in well-informed patients who do not wish to have or are not suitable for oral vasoactive therapy; • who are vasculogenic ED patients who are poor responders to PDE5Is	Weak
Use vacuum erection devices in well-informed patients requesting non-invasive, drug-free management of ED.	Weak
Implant a penile prosthesis if other treatments fail or depending upon patient preference. Patients should be fully informed of the benefits and harms associated with the procedure.	Strong
Start pro-erectile treatments at the earliest opportunity after radical prostatectomy/pelvic surgery and other curative treatments for PCa.	Weak

5.7 *Follow-up*

Follow-up is important in order to assess the 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.

6. DISORDERS OF EJACULATION

6.1 Introduction

Ejaculation is a complex physiological process that comprises emission and expulsion processes and is mediated by interwoven neurological and hormonal pathways [531]. Any interference with those pathways may cause a wide range of ejaculatory disorders. The spectrum of ejaculation disorders includes premature ejaculation (PE), retarded or delayed ejaculation, anejaculation, painful ejaculation, retrograde ejaculation, anorgasmia and haemospermia.

6.2 Premature ejaculation

6.2.1 Epidemiology

Historically, the main problem in assessing the prevalence of PE has been the lack of a universally recognised definition at the time that surveys were conducted [532]. See Section 4.2 for a comprehensive discussion of the epidemiology of PE.

6.2.2 Pathophysiology and risk factors

The aetiology of PE is relatively unknown, with limited data to support suggested biological and psychological hypotheses, including anxiety [533-536], penile hypersensitivity [537-544] and 5-hydroxytryptamine (HT) receptor dysfunction [545-550]. The classification of PE into four subtypes [201] has contributed to a better delineation of lifelong, acquired, variable and subjective PE [551-553]. It has been hypothesised that the pathophysiology of lifelong PE is mediated by a complex interplay of central and peripheral serotonergic, dopaminergic, oxytocinergic, endocrinological, genetic and epigenetic factors [554]. Acquired PE may occur due to psychological problems - such as sexual performance anxiety, and psychological or relationship problems and/or co-morbidity, including ED, prostatitis, hyperthyroidism and poor sleep quality [555-558]. Variable PE is considered to be a normal variation of sexual function whereas subjective PE can stem from cultural or abnormal psychological constructs [201].

A significant proportion of men with ED also experience PE [205, 559]. 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 National Health and Social Life Survey (NHSLS), the prevalence of PE is not affected by age [197], unlike ED, which increases with age. Premature ejaculation is not affected by marital or income status [197, 560].

However, PE is more common in Black men, Hispanic men, and men from regions where an Islamic background is common [197, 561, 562] and the prevalence may be higher in men with a lower educational level [197, 205]. Other reported risk factors for PE include genetic predisposition [550, 563-566], poor overall health status and obesity [197], prostate inflammation [567-571], hyperthyroidism [555], low prolactin levels [572], high testosterone levels [573], vitamin D and B12 deficiency [574, 575], diabetes [576, 577], MetS [578, 579], lack of physical activity [580], emotional problems and stress [197, 581, 582], depressive symptoms [582], and traumatic sexual experiences [197, 205].

*6.2.3 **Impact of PE on quality of life***

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 [583-585]. Premature ejaculation can have a detrimental effect on self-confidence and the relationship with the partner, and may sometimes cause mental distress, anxiety, embarrassment and depression [583, 586, 587]. Moreover, PE may also affect the partner's sexual functioning and their satisfaction with the sexual relationship decreases with increasing severity of the patient's condition [588-590]. Despite the possible serious psychological and QoL consequences of PE, few men seek treatment [198, 205, 591-594].

*6.2.4 **Classification***

There is still little consensus about the definition and classification of PE [595]. It is now universally accepted that "premature ejaculation" is a broad term that includes several concepts belonging to the common category of PE. The most recent definition comes from the International Classification of Diseases 11th Revision, where PE was renamed as Early Ejaculation [596]: *"Male early ejaculation is characterized by ejaculation that occurs prior to or within a very short duration of the initiation of vaginal penetration or other relevant sexual stimulation, with no or little perceived control over ejaculation. The pattern of early ejaculation has occurred episodically or persistently over a period of at least several months and is associated with clinically significant distress."*

This definition includes four categories: male early ejaculation, lifelong generalised and situational, acquired generalised and situational, and unspecified.

> The Diagnostic and Statistical Manual of Mental Disorders V (DSM-V) [207] and the International Society for Sexual Medicine (ISSM) [597] published definitions for lifelong and acquired PE. These definitions are overlapping, with 3 shared factors (1. Time to ejaculation assessed by IELT; 2. Perceived control; and, 3. Distress, bother, frustration, interpersonal difficulty related to the ejaculatory dysfunction), resulting in a multi-dimensional diagnosis [597].

Two more PE syndromes have been proposed [552]:

- '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 [598].

*6.2.5 **Diagnostic evaluation***

Diagnosis of PE is based on the patient's medical and sexual history [599-602]. 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 [559, 603]. Furthermore, some patients are unaware that loss of erection after ejaculation is normal and may erroneously complain of ED, while the actual problem is PE [594].

6.2.5.1 Intravaginal ejaculatory latency time (IELT)

Although it has been suggested as an objective diagnostic criterion and treatment outcome measure [604, 605], the use of IELT alone is not sufficient to define PE, as there is significant overlap between men with and without PE [606, 607]. Moreover, some men may experience PE in their non-coital sexual activities (e.g., during masturbation, oral sex or anal intercourse); thus, measuring IELT will not be suitable for their assessment. Although PE is apparently less prevalent and less bothersome among men who have sex with men (MSM) [608], many of them may also suffer from PE and IELT cannot be applied to them [609, 610]. Although some studies demonstrated that MSM report longer ejaculation latency time compared to straight men [608], some others failed to demonstrate such a difference [611].

In everyday clinical practice, self-estimated IELT is sufficient [612]. Self-estimated and stopwatch-measured IELT are interchangeable and correctly assign PE status with 80% sensitivity and 80% specificity [613].

Measurement of IELT with a calibrated stopwatch is mandatory in clinical trials. For any drug treatment study of PE, Waldinger *et al.,* suggested using geometric mean instead of arithmetic mean IELT because the distributed IELT data are skewed. Otherwise, any treatment-related ejaculation delay may be overestimated if the arithmetic mean IELT is used instead of the geometric mean IELT [614].

6.2.5.2 Premature ejaculation assessment questionnaires

The need to objectively assess PE has led to the development of several questionnaires based on using PROMs. Only two questionnaires can discriminate between patients who have PE and those who do not:

- Premature Ejaculation Diagnostic Tool (PEDT): A five-item questionnaire based on focus groups and interviews from the USA, Germany, and Spain assesses control, frequency, minimal stimulation, distress and interpersonal difficulty [615]. A total score of > 11 suggests a diagnosis of PE, 9 or 10 suggests a probable diagnosis, and < 8 indicates a low likelihood of PE.

- Arabic Index of Premature Ejaculation (AIPE): A seven-item questionnaire developed in Saudi Arabia assesses sexual desire, hard erections for sufficient intercourse, time to ejaculation, control, satisfaction of the patient and partner, and anxiety or depression [616]. A cut-off score of 30 (range 7-35) discriminates PE diagnosis best. The severity of PE is classified as severe (score: 7-13), moderate (score: 14-19), mild-to-moderate (score: 20-25) and mild (score: 26-30).

Other questionnaires used to characterise PE and determine treatment effects include the Premature Ejaculation Profile (PEP) [607], Index of Premature Ejaculation (IPE) [617] and Male Sexual Health Questionnaire Ejaculatory Dysfunction (MSHQ-EjD) [618]. Currently, their role is optional in everyday clinical practice. The Masturbatory Premature Ejaculation Diagnostic Tool (MPEDT) has also been recently proposed [619], due to fact since PE patients report longer IELTs and lesser bother/distress during masturbation than partnered sex [620]; however, further validation studies are required before the routine use of this questionnaire in this population.

6.2.5.3 Physical examination and investigations

Physical examination may be part of the initial assessment of men with PE. It may include a focused examination of the urological, 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 [601].

6.2.5.4 Recommendations for the diagnostic evaluation of PE

Summary of evidence	**LE**
A comprehensive medical history and a thorough physical examination can serve as valuable tools for clinicians in identifying the underlying medical factors contributing to PE.	3
PE can negatively impact self-confidence, strain partner relationships, and potentially lead to emotional distress, anxiety, shame, and depression.	2a
Several questionnaires can be used for the diagnosis of PE (PEDT, AIPE) and for assessing the therapeutic outcomes of PE interventions (PEP).	2b
Although relying on IELT is inadequate for characterizing PE, self-reported IELT proves satisfactory in routine clinical contexts.	3

Recommendations	**Strength rating**
Perform the diagnosis and classification of premature ejaculation (PE) based on medical and sexual history, which should include assessment of intravaginal ejaculatory latency time (IELT) (self-estimated), perceived control, distress and interpersonal difficulty due to the ejaculatory dysfunction.	Strong
Use patient-reported outcomes in daily clinical practice.	Weak

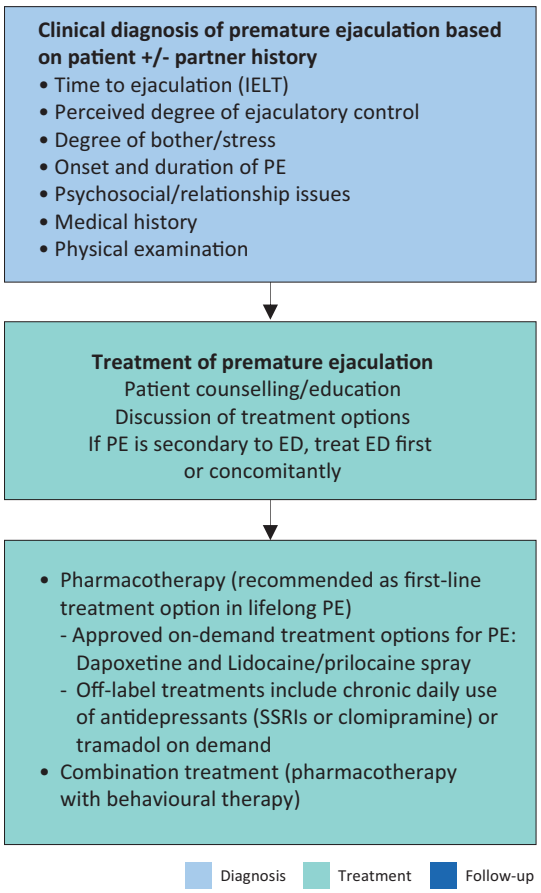
Include physical examination in the initial assessment of PE to identify anatomical abnormalities that may be associated with PE or other sexual dysfunctions, particularly erectile dysfunction.	Strong
Do not perform routine laboratory or physiological tests. They should only be directed by specific findings from history or physical examination.	Strong

6.2.6 Disease management

Before commencing any treatment, it is essential to define the subtype of PE and discuss patient's expectations thoroughly. Pharmacotherapy must be considered the first-line treatment for patients with lifelong PE, whereas treating the underlying cause (e.g., ED, prostatitis, LUTS, anxiety and hyperthyroidism) must be the initial goal for patients with acquired PE [601]. Various behavioural techniques may be beneficial in treating variable and subjective PE [621]. Psychotherapy can also be considered for PE patients who are uncomfortable with pharmacological therapy or in combination with pharmacological therapy [622, 623]. However, there is weak and inconsistent evidence regarding the effectiveness of these psychosexual interventions and their long-term outcomes in PE are unknown [624].

Dapoxetine (30 and 60 mg) is the first on-demand oral pharmacological agent approved for lifelong and acquired PE in many countries, except for the USA [625]. The metered-dose aerosol spray of lidocaine (150 mg/mL) and prilocaine (50 mg/mL) combination is the first topical formulation to be officially approved for on-demand treatment of lifelong PE by the EMA in the European Union [626]. All other medications used in PE are off-label indications [627]. In this context, daily or on-demand use of selective serotonin re-uptake inhibitors (SSRIs) and clomipramine and on-demand topical anaesthetic agents have consistently shown efficacy in PE [628-631]. The long-term outcomes of 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 6).

Figure 6: Management of premature ejaculation*

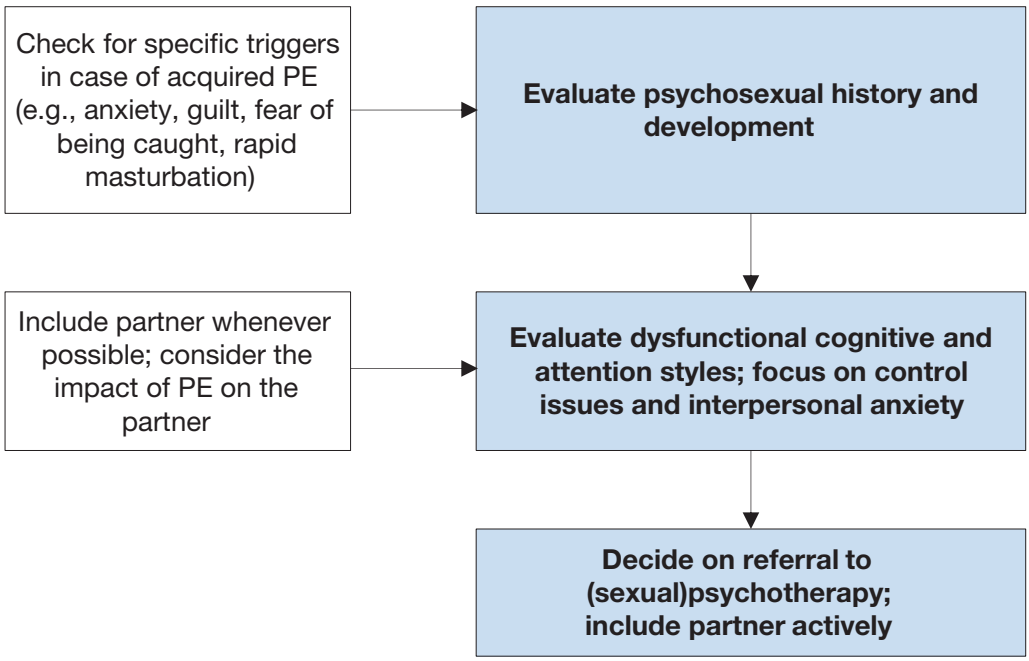


ED = erectile dysfunction; PE = premature ejaculation; IELT = intravaginal ejaculatory latency time; SSRI = selective serotonin receptor inhibitor.

6.2.6.1 Psychological aspects and intervention

Psychosexual interventions, whether behavioural, cognitive, or focused on the couple, are aimed at teaching techniques to control/delay ejaculation, gaining confidence in sexual performance, reducing anxiety, and promoting communication and problem-solving within the couple [621]. Interventions with a focus on sexual education or acceptance may be positive as well [632]. However, psychosexual interventions alone regarding PE lack empirical support. Recent evidence suggests that start-stop exercises, combined with psycho-education and mindfulness techniques improve PE symptoms, as well as PE-associated distress, anxiety and depression [633]. The potential benefits of mindfulness have been reported [634]. Behavioural therapy may be most effective when used to 'add value' to medical interventions. Smartphone-delivered psychological intervention, aimed at improving behavioural skills for ejaculatory delay and sexual self-confidence, has positive effects, supporting E-health in the context of PE [635].

Figure 7: Key aspects of psychosexual evaluation



6.2.6.1.1 Summary of evidence and recommendations for the assessment and treatment (psychosexual approach) of PE

Summary of evidence	**LE**
The incorporation of a psychosexual approach, alongside psycho-educational guidance and mindfulness techniques, ameliorates symptoms of PE and alleviate the associated distress, anxiety, and depression.	2b
The combination of psychosexual approaches and pharmacological treatments yields superior outcomes compared to pharmacological interventions alone.	3

Recommendations for assessment	**Strength rating**
Assess sexual history and psychosexual development.	Strong
Assess anxiety, and interpersonal anxiety; focus on control issues.	Strong
Include the partner if available; check for the impact of PE on the partner.	Strong
Recommendations for treatment (psychosexual approach)	
Use behavioural, cognitive and/or couple therapy approaches in combination with pharmacotherapy. Discuss the use of mindfulness exercises.	Weak

6.2.6.2 Pharmacotherapy

6.2.6.2.1 Dapoxetine

Dapoxetine hydrochloride is a short-acting SSRI with a pharmacokinetic profile suitable for on-demand treatment for PE [636]. It has a rapid T_{max} (1.3 hours) and a short half-life (95% clearance rate after 24 hours) [637, 638]. 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 a baseline average IELT < 30 seconds [639].

In RCTs, dapoxetine, 30 mg or 60 mg 1-2 hours before intercourse, was effective at improving IELT and increasing ejaculatory control, decreasing distress, and increasing satisfaction [639]. Dapoxetine has shown a similar efficacy profile in men with lifelong and acquired PE [639, 640]. Treatment-related adverse effects were dose-dependent and included nausea, diarrhoea, thirst, headache and dizziness [640]. Treatment-emergent adverse events (TEAEs) were responsible for study discontinuation in 4% (30 mg) and 10% (60 mg) of subjects [612]. There was no indication of an increased risk of suicidal ideation or suicide attempts and little indication of withdrawal symptoms with abrupt dapoxetine cessation [639, 640]. Dapoxetine is safer than formal anti-depressant compounds used for treatment of PE [641].

A low rate (0.1%) of vasovagal syncope was reported in phase 3 studies [642]. According to the summary of product characteristics, vital orthostatic signs (blood pressure and heart rate) must be measured prior to starting dapoxetine, and dose titration must be considered [643]. The EMA assessment report for dapoxetine concluded that the potentially increased risk for syncope had been proven manageable with adequate risk minimisation measures [644]. No cases of syncope were observed in a post-marketing observational study, which identified patients at risk for the orthostatic reaction using the patient's medical history and orthostatic testing [645].

Many patients and physicians may prefer using dapoxetine in combination with a PDE5I to extend the time until ejaculation and minimise the risk of ED due to dapoxetine treatment. Phase 1 studies of dapoxetine have confirmed that it has no pharmacokinetic interactions with PDE5Is (i.e., tadalafil 20 mg and sildenafil 100 mg) [646]. When dapoxetine is co-administered with PDE5Is, it is well tolerated, with a safety profile consistent with previous phase 3 studies of dapoxetine alone [647]. An RCT, including PE patients without ED, demonstrated that a combination of dapoxetine with sildenafil could significantly improve IELT values and PROs compared with dapoxetine alone or sildenafil alone, with tolerable adverse events [648]. The efficacy and safety of dapoxetine/sildenafil combination tablets for the treatment of PE have also been reported [649].

The discontinuation rates of dapoxetine seem moderate to high [650]. The cumulative discontinuation rates increase over time, reaching 90% at two years after initiation of therapy. The reasons for the high discontinuation rate are cost (29.9%), disappointment that PE was not curable and the on-demand nature of the drug (25%), adverse effects (11.6%), perceived poor efficacy (9.8%), a search for other treatment options (5.5%), and unknown (18.3%) [651]. Similarly, it was confirmed that many patients on dapoxetine treatment spontaneously discontinued treatment, while this rate was reported at 50% for other SSRIs and 28.8% for paroxetine, respectively [652]. In a Chinese cohort study, 13.6% of the patients discontinued dapoxetine due to lack of efficacy (62%), adverse effects (24%), and low frequency of sexual intercourse (14%) [653].

6.2.6.2.2 Off-label use of antidepressants

Selective serotonin re-uptake inhibitors are used to treat mood disorders but can delay ejaculation and therefore have been widely used 'off-label' for PE since the 1990s [654-656]. Commonly used SSRIs include continuous intake of citalopram, fluoxetine, fluvoxamine, paroxetine and sertraline, all of which have similar efficacy, whereas paroxetine exerts the most substantial ejaculation delay [604, 657, 658]. A novel 5-HT1A receptor antagonist, GSK958108, significantly delayed ejaculation in a double-blind, placebo-controlled trial [659].

Clomipramine, the most serotoninergic tricyclic antidepressant, was first reported in 1977 as an effective PE treatment [660, 661]. In an RCT, on-demand use of clomipramine 15 mg, two to six hours before sexual intercourse was found to be associated with IELT fold change and significant improvements in PRO measures in the treatment group as compared with the placebo group (4.66 ± 5.64 vs. 2.80 ± 2.19, $P < 0.05$) [662, 663]. The most commonly reported TEAEs were nausea in 15.7% and dizziness in 4.9% of men, respectively [662, 663].

Several meta-analyses suggest SSRIs may increase the geometric mean IELT by 2.6-13.2-fold [664]. Paroxetine is superior to fluoxetine, clomipramine and sertraline [665, 666]. Sertraline is superior to fluoxetine, whereas the efficacy of clomipramine is not significantly different from that of 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 [664-666].

Ejaculation delay may start a few days after drug intake, but it is more evident after one to two weeks as 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 [660]. Common TEAEs of SSRIs include fatigue, drowsiness, yawning, nausea, vomiting, dry mouth, diarrhoea and perspiration; TEAEs are usually mild and gradually improve after two to three weeks of treatment [660, 667]. Decreased libido, anorgasmia, anejaculation and ED have also been reported.

Because of the risk of suicidal ideation or suicide attempts, caution is suggested in prescribing SSRIs to young adolescents aged ≤ 18 years with PE, and to men with PE and a comorbid depressive disorder, particularly when associated with suicidal ideation. Patients should be advised to avoid sudden cessation or rapid dose reduction of daily-dosed SSRIs, which may be related to SSRI withdrawal syndrome [612]. Moreover, PE patients trying to conceive should avoid using these medications because of their detrimental effects on sperm cells [668-672].

6.2.6.2.3 Topical anaesthetic agents

The use of local anaesthetics to delay ejaculation is the oldest form of pharmacological therapy for PE [673]. Several trials [540, 675] 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. Meta-analyses have confirmed the efficacy and safety of these agents for the treatment of PE [676]. In a meta-analysis, the efficacy of local anaesthetics was best among the other treatment options including SSRIs, dapoxetine 30 and 60 mg, PDE5Is and tramadol for < 8 weeks of therapy [676].

6.2.6.2.3.1 Lidocaine/prilocaine cream

Lidocaine/prilocaine creams can significantly increase the stopwatch-measured IELT from 1-2 minutes to 6-9 minutes [677, 678]. Although no significant TEAEs have been reported, topical anaesthetics are contraindicated in patients or partners with an allergy to any ingredient in the product. These anaesthetic creams/gels may be transferred to the partner, resulting in vaginal numbness. Therefore, patients are advised to use a condom after applying the cream to their penis. Alternatively, the penis can be washed to clean off any residual active compound prior to sexual intercourse. Since these chemicals may be associated with cytotoxic effects on fresh human sperm cells, couples seeking parenthood should not use topical lidocaine/prilocaine-containing substances [679].

6.2.6.2.3.2 Lidocaine/prilocaine spray

The eutectic lidocaine/prilocaine spray is a metered-dose aerosol spray containing purely base forms of lidocaine (150 mg/mL) and prilocaine (50 mg/mL), which has been officially approved by the EMA for the treatment of lifelong PE [680]. Compared to topical creams, the metered-dose spray delivery system has been proved to deposit the drug in a dose-controlled, concentrated film covering the glans penis, maximising neural blockage and minimising the onset of numbness [681], without absorption through the penile shaft skin [682].

Several studies have demonstrated the efficacy of lidocaine/prilocaine spray in improving both IELT and PROs three sprays administered 5 minutes before sexual intercourse [683, 684]. Published data showed that lidocaine/prilocaine spray increases IELT over time up to 6.3-fold over three months, with a month-by-month improvement through the course of the treatment in long-term studies [685]. A low incidence of local TEAEs in both patients and partners has been reported, including genital hypoaesthesia (4.5% and 1.0% in men and female partners, respectively) and ED (4.4%), and vulvovaginal burning sensation (3.9%), but is unlikely to be associated with systemic TEAEs [686, 687].
Lidocaine-only sprays are also available and found to be effective in the treatment of PE [688, 689].

6.2.6.2.4 Tramadol

Tramadol is a centrally-acting analgesic agent that combines opioid receptor activation and serotonin and noradrenaline re-uptake inhibition. Tramadol is a mild-opioid receptor agonist, but it also displays antagonistic properties on transporters of noradrenaline and 5-HT [690]. This mechanism of action distinguishes tramadol from other opioids, including morphine. Tramadol is readily absorbed after oral administration and has an elimination half-life of 5-7 hours.

Several clinical trials evaluated the efficacy and safety of tramadol ODT (62 and 89 mg) and tramadol HCl in the treatment of PE [691]. Up to 2.5-fold increases in the median IELT have been reported among patients who received on-demand tramadol treatment [692, 693].

Adverse effects were reported at doses used for analgesic purposes (≤ 400 mg daily) and included constipation, sedation and dry mouth. In May 2009, the US FDA released a warning letter about tramadol's potential to cause addiction and difficulty in breathing [694]. The tolerability during the twelve-week study period in men with PE was acceptable [695]. Several other studies have also reported that tramadol exhibits a significant dose-related efficacy along with potential adverse effects during the treatment of PE [692, 693]. The Guidelines Panel considers tramadol as a potential alternative treatment to established first-line therapeutic options in men with PE; however, it should be clearly outlined that the use of tramadol has to be considered with caution since there is a lack of data on the long-term safety of the compound in this setting.

6.2.6.2.5 Phosphodiesterase type 5 inhibitors

Although IELT was not significantly improved, sildenafil increased confidence, the perception of ejaculatory control and overall sexual satisfaction, reduced anxiety and the refractory time to achieve a second erection after ejaculation [696, 697]. Several open-label studies have shown that a combination of PDE5Is and SSRIs is superior to SSRI monotherapy, which has also been recently confirmed by a Bayesian network meta-analysis [676, 698].

6.2.6.2.6 Other drugs

In addition to the aforementioned drugs, there is continuous research into other treatment options. Considering the abundant α1a-adrenergic receptors in seminal vesicles and the prostate and the role of the sympathetic system in ejaculation physiology, the efficacy of selective α-blockers in the treatment of PE has been assessed [699-701]. A study demonstrated that the wake-promoting agent modafinil may be effective in delaying ejaculation and improving PROMs [702]. Decreasing penile sensitivity with glans penis augmentation using hyaluronic acid for the treatment of PE was initially proposed by Korean researchers in 2004 [703]. Since then, it has gained popularity mainly in Asian countries [704, 705]. Randomised controlled studies demonstrated that hyaluronic acid glans injections were safe, with a modest but significant increase in IELT along with improvements in PRO measures [704, 705]. No serious TEAEs were reported related to glans penis injections with hyaluronic acid. However, this procedure may result in serious complications, and more safety studies must be conducted before recommending this treatment to PE patients [706]. Selective dorsal neurectomy has also been suggested for the treatment of PE, mainly by Asian researchers [707-713]. However, considering the irreversible nature of these procedures, more safety data are warranted.

Considering the importance of central oxytocin receptors in the ejaculation reflex, several researchers have assessed the efficacy and safety of oxytocin receptor antagonists in the treatment of PE [714]. Epelsiban [715] and cligosiban [716-719] have been found to be safe and mildly effective in delaying ejaculation, but further controlled trials are needed [718, 719]. Delayed ejaculation was associated with the use of pregabalin, a new generation of gabapentinoids, as a side-effect. On-demand oral pregabalin 150 mg was found to increase the IELTs of patients 2.45 ± 1.43-fold. Treatment-emergent side effects (blurred vision, dizziness, vomiting) were minimal and did not lead to drug discontinuation [720].

The role of other proposed treatment modalities for the treatment of PE, such as penis-root masturbation [721], vibrator-assisted start-stop exercises [633], transcutaneous functional electric stimulation [722, 723], transcutaneous posterior tibial nerve stimulation [724], acupuncture [725-727] and practising yoga [728] need more evidence to be considered in the clinical setting.

*6.2.7 **Summary of evidence and recommendations for the treatment of PE***

Summary of evidence	**LE**
Pharmacotherapy includes either dapoxetine on-demand (an oral short-acting SSRI) and eutectic lidocaine/prilocaine spray (a topical desensitising agent), which are the only approved treatments for PE, or other off-label antidepressants (daily/on-demand SSRIs and clomipramine).	1a
Both on-demand dapoxetine treatment and daily SSRI treatment improve IELT values significantly.	1a
Both on-demand dapoxetine treatment and daily SSRI treatment have generally tolerable side effects when used for the treatment of PE.	1a
Daily/on-demand clomipramine treatments improve IELT values significantly and have generally tolerable side effects when used for the treatment of PE.	1a
Cream and spray forms of lidocaine/prilocaine improve IELT values significantly and have safe a profile.	1b
Tramadol is effective in the treatment of PE but the evidence is still inadequate for its long-term safety profile including addiction potential.	1a

Combination of PDE5Is and SSRIs overtakes SSRI monotherapy in effectiveness.	1a
Hyaluronic acid injections are effective in decreasing penile sensitivity.	2b

Recommendations for assessment	Strength rating
Treat erectile dysfunction (ED), other sexual dysfunction or genitourinary infection (e.g., prostatitis) first.	Strong
Use either dapoxetine or the lidocaine/prilocaine spray as first-line treatments for lifelong premature ejaculation (PE).	Strong
Use off-label oral treatment with daily selective serotonin re-uptake inhibitor (SSRIs) or daily/on-demand clomipramine as a viable alternative for second-line treatments.	Strong
Use off-label tramadol with caution as a viable on-demand third-line treatment alternative to on-demand/daily antidepressants (SSRIs or clomipramine).	Strong
Use PDE5Is alone or in combination with other therapies in patients with PE (without ED).	Strong
Use psychological/behavioural therapies in combination with pharmacological treatment in the management of acquired PE.	Weak
Use hyaluronic acid injection with caution as a treatment option for PE compared to other more established treatment modalities.	Weak
Do not perform dorsal neurectomy because more safety data are warranted.	Weak

6.3 Delayed Ejaculation (DE)

6.3.1 ***Definition and classification***

The American Psychiatric Association defines DE as requiring one of two symptoms; marked delay, infrequency or absence of ejaculation on 75-100% of occasions that persists for at least 6 months and causes personal distress [207]. However, in a recent study, while ejaculatory latency and control were significant criteria to differentiate men with DE from those without ejaculatory disorders, bother/distress did not emerge as a significant factor [729]. Similar to PE, there are distinctions among lifelong, acquired and situational DE [207]. A study demonstrated that men with lifelong DE are younger, report greater DE symptomatology, are less likely to have a medical issue or medication that can cause DE and are more likely to masturbate for anxiety/distress reduction than for pleasure as compared with men with acquired delayed ejaculation [730]. Although the evidence is limited, the prevalence of lifelong and acquired DE is estimated at around 1% and 4%, respectively [208].

6.3.2 ***Pathophysiology and risk factors***

The aetiology of DE can be psychological, organic (e.g., incomplete spinal cord lesion or iatrogenic penile nerve damage), or pharmacological (e.g., SSRIs, antihypertensive drugs, or antipsychotics) [731, 732] (Table 18). Other factors that may play a role in the aetiology of DE include tactile sensitivity and tissue atrophy [632]. Although low testosterone level has been considered a risk factor in the past [573, 733], more contemporary studies have not confirmed any association between ejaculation times and serum testosterone levels [734, 735]. Idiosyncratic masturbation and lack of desire for stimuli are also proposed risk factors for DE [736-738].

Table 13: Aetiological causes of delayed ejaculation and anejaculation [739-742]

Ageing Men	Degeneration of penile afferent nerves inhibited ejaculation
Congenital	Mullerian duct cyst Wolfian duct abnormalities Prune Belly Syndrome Imperforate Anus Genetic abnormalities
Anatomic causes	Transurethral resection of prostate Bladder neck incision Circumcision Ejaculatory duct obstruction (can be congenital or acquired)

Neurogenic causes	Diabetic autonomic neuropathy Multiple sclerosis Spinal cord injury Radical prostatectomy Proctocolectomy Bilateral sympathectomy Abdominal aortic aneurysmectomy Para-aortic lymphadenectomy
Infective/Inflammation	Urethritis Genitourinary tuberculosis Schistosomiasis Prostatitis Orchitis
Endocrine	Hypogonadism Hypothyroidism Prolactin disorders Disorders of lipid metabolism
Medication	Antihypertensives; thiazide diuretics Alpha-adrenergic blockers Antipsychotics and antidepressants Alcohol Antiandrogens Ganglion blockers
Psychological	Anxiety Psychoses Acute psychological distress Relationship distress Psychosexual skill deficit Disconnect between arousal and sexual situations Masturbation style

*6.3.3 **Investigation and treatment***

Patients should have a full medical and sexual history performed along with a detailed physical examination when evaluating for DE. Understanding the details of the ejaculatory response, sensation, frequency, and sexual activity/techniques; cultural context and history of the disorder; quality of the sexual response cycle (desire, arousal, ejaculation, orgasm, and refractory period); partner's assessment of the disorder and if the partner suffers from any sexual dysfunction her/himself; and the overall satisfaction of the sexual relationship are all important to garner during history-taking [602]. It is incumbent on the clinician to diagnose medical pathologies that cause or contribute to DE, such as assessing the hormonal milieu, anatomy, and overall medical condition.

6.3.3.1 Psychological aspects and intervention

There is scarce literature on the psychological aspects relating to DE, as well as on empirical evidence regarding psychological treatment efficacy. Studies on psychological aspects have revealed that men with DE show a strong need to control their sexual experiences. Delayed ejaculation is associated with difficulties surrendering to sexual pleasure during sex - i.e., the sense of *letting go* [743] - which denotes a underlying psychological mechanism influencing the reaching of orgasm [744]. As for psychological treatments, these may include, but are not limited to: increased genital-specific stimulation; sexual education; role-playing on his own and in front of his partner; retraining masturbatory practices; anxiety reduction on ejaculation and performance; and, re-calibrating the mismatch of sexual fantasies with arousal (such as with pornography use and fantasy stimulation compared to reality). Masturbation techniques that are either solo or partnered can be considered practice for the "real performance", which can eventually result in greater psychosexual arousal and orgasm for both parties [738]. Although masturbation with fantasy can be harmful when not associated with appropriate sexual arousal and context, fantasy can be supportive if it allows blockage of critical thoughts that may prevent orgasm and ejaculation. Techniques geared towards reducing anxiety are important skills that can help overcome performance anxiety, as this can often interrupt the natural erectile function through orgasmic progression. Referral to a sexual therapist, psychologist or psychiatrist is appropriate and often warranted.

6.3.3.2 *Pharmacotherapy*

Several pharmacological agents, including cabergoline, bupropion, alpha-1-adrenergic agonists (pseudoephedrine, midodrine, imipramine and ephedrine), buspirone, oxytocin, testosterone, bethanechol, yohimbine, amantadine, cyproheptadine and apomorphine have been used to treat DE with varied success [632]. Unfortunately, there is no FDA or EMA-approved medications to treat DE, as most of the cited research is based on case-cohort studies that were not randomised, blinded, or placebo-controlled. Many drugs have been used as primary treatments and/or antidotes to other medications that can cause DE. A survey of sexual health providers demonstrated an overall treatment success of 40% with most providers commonly using cabergoline, bupropion or oxytocin [745]. However, this survey measured the anecdotal results of practitioners. There was no proven efficacy or superiority of any drug due to a lack of placebo-controlled, randomised, blinded, comparative trials [739]. In addition to pharmacotherapy, penile vibratory stimulation (PVS) is also used as an adjunct therapy for DE [746]. Another study that used combined therapy of midodrine and PVS to increase autonomic stimulation in 158 men with spinal cord injury led to ejaculation in almost 65% of the patients [747].

Summary of evidence	**LE**
Delayed ejaculation can be caused by several aetiologies including congenital, anatomic, neurogenic, infective, hormonal, drug-related and psychological.	3
There is not enough evidence to support a definitive treatment for DE.	3

6.4 Anejaculation

6.4.1 ***Definition and classification***

Anejaculation involves the complete absence of antegrade or retrograde ejaculation. It is caused by the failure of semen emission from the seminal vesicles, prostate, and ejaculatory ducts into the urethra [748]. True anejaculation is usually associated with a normal orgasmic sensation and is always associated with central or peripheral nervous system dysfunction or with drugs [749].

6.4.2 ***Pathophysiology and risk factors***

Generally, anejaculation shares similar aetiological factors with DE and retrograde ejaculation (Table 13).

6.4.3 ***Investigation and treatment***

Drug treatment for anejaculation caused by lymphadenectomy and neuropathy, or psychosexual therapy for anorgasmia, is not effective. In all these cases, and in men who have a spinal cord injury, PVS (i.e., application of a vibrator to the penis) is the first-line therapy. In anejaculation, PVS evokes the ejaculation reflex [750], which requires an intact lumbosacral spinal cord segment. If the quality of semen is poor or ejaculation is retrograde, the couple may enter an *in vitro* fertilisation program whenever fathering is desired. If PVS has failed, electro-ejaculation can be the therapy of choice [751]. Other sperm-retrieval techniques may be used when electro-ejaculation fails or cannot be carried out [752]. Anejaculation following either retroperitoneal surgery for testicular cancer or total mesorectal excision can be prevented using unilateral lymphadenectomy or autonomic nerve preservation [753], respectively.

6.5 Painful Ejaculation

6.5.1 ***Definition and classification***

Painful ejaculation is a condition in which a patient feels mild discomfort to severe pain during or after ejaculation. The pain can involve the penis, scrotum, and perineum [754].

6.5.2 ***Pathophysiology and risk factors***

Many medical conditions can result in painful ejaculation, but it can also be an idiopathic problem. Initial reports demonstrated possible associations of painful ejaculation with calculi in the seminal vesicles [755], sexual neurasthenia [756], sexually transmitted diseases (STIs) [754, 757], inflammation of the prostate [228, 758], PCa [759, 760], BPH [226], prostate surgery [761, 762], pelvic radiation [763], herniorrhaphy [764] and antidepressants [765-767]. Further case reports have suggested that mercury toxicity or Ciguatera toxin fish poisoning may also result in painful ejaculation [768, 769]. Psychological issues may also be the cause of painful ejaculation, especially if the patient does not experience this problem during masturbation [770].

6.5.3 ***Investigation and treatment***

Treating painful ejaculation must be tailored to the underlying cause if detected. Psychotherapy or relationship counselling, withdrawal of suspected agents (drugs, toxins, or radiation) [765, 766, 771] or the prescription of appropriate medical treatment (antibiotics, α-blockers or anti-inflammatory agents) may ameliorate painful ejaculation. Behavioural therapy, muscle relaxants, antidepressant treatment, anticonvulsant drugs and/or opioids, and pelvic floor exercises, may be implemented if no underlying cause can be identified [772, 773].

6.5.3.1 Surgical intervention

If medical treatments fail, surgical operations such as TURP, transurethral resection of the ejaculatory duct (TURED) and neurolysis of the pudendal nerve have been suggested [774, 775]. However, there is no strong supporting evidence that surgical therapy improves painful ejaculation: therefore, it must be used with caution.

6.6 Retrograde ejaculation

*6.6.1 **Definition and classification***

Retrograde ejaculation is the total, or sometimes partial, absence of antegrade ejaculation, due to semen passing backwards through the bladder neck into the bladder. Patients may experience a normal or decreased orgasmic sensation. The causes of retrograde ejaculation can be divided into neurogenic, pharmacological, urethral, or bladder neck incompetence [754].

*6.6.2 **Pathophysiology and risk factors***

The process of ejaculation requires complex co-ordination and interplay between the epididymis, vas deferens, prostate, seminal vesicles, bladder neck and bulbourethral glands [776]. Upon ejaculation, sperm are rapidly conveyed along the vas deferens and into the urethra via the ejaculatory ducts. From there, the semen progresses in an antegrade fashion, partly maintained by coaptation of the bladder neck and rhythmic contractions of the periurethral muscles, co-ordinated by a centrally mediated reflex [776]. Closure of the bladder neck and seminal emission is initiated via the sympathetic nervous system from the lumbar sympathetic ganglia and subsequently hypogastric nerve. Prostatic and seminal vesicle secretion, as well as contraction of the bulbo-cavernosal, ischio-cavernosal and pelvic floor muscles are initiated by the S 2-4 parasympathetic nervous system via the pelvic nerve [776].

Any factor that disrupts this reflex and inhibits contraction of the bladder neck (internal vesical sphincter) may lead to retrograde passage of semen into the bladder. These can be broadly categorised as pharmacological, neurogenic, anatomic and endocrinal causes of retrograde ejaculation (Table 14).

Table 14: Aetiology of retrograde ejaculation [754]

Neurogenic	Spinal cord injury Cauda equina lesions Multiple sclerosis Autonomic neuropathy Retroperitoneal lymphadenectomy Sympathectomy or aortoiliac surgery Prostate, colorectal and anal surgery Parkinson´s disease Diabetes mellitus Psychological/behavioural
Urethral	Ectopic ureterocele Urethral stricture Urethral valves or verumontaneum hyperplasia Congenital dopamine β-hydroxylase deficiency
Pharmacological	Antihypertensives, thiazide diuretics α-1-Adrenoceptor antagonists Antipsychotics and antidepressants
Endocrine	Hypothyroidism Hypogonadism Hyperprolactinaemia
Bladder neck incompetence	Congenital defects/dysfunction of hemitrigone Bladder neck resection (transurethral resection of the prostate) Prostatectomy

6.6.3 ***Disease management***

6.6.3.1 Pharmacological

Sympathomimetics stimulate the release of noradrenaline and activate α- and β-adrenergic receptors, resulting in the closure of the internal urethral sphincter, restoring the antegrade flow of semen. The most common sympathomimetics are synephrine, pseudoephedrine hydrochloride, ephedrine, phenylpropanolamine and midodrine [777]. Unfortunately, as time progresses, their effect diminishes [778]. Many studies published about the efficacy of sympathomimetics in the treatment of retrograde ejaculation suffer from small sample size, with some represented by case reports.

An RCT randomised patients to receive one of four α-adrenergic agents (dextroamphetamine, ephedrine, phenylpropanolamine and pseudoephedrine) with or without histamine. The patients suffered from failure of ejaculation following retroperitoneal lymphadenectomy. They found that four days of treatment prior to ejaculation was the most effective and that all the adrenergic agonists restored antegrade ejaculation [777]. In a systematic review, the efficacy of this group of medications was found to be 28% [211]. The adverse effects of sympathomimetics include dryness of mucous membranes and hypertension.

The use of antimuscarinics has been described, including brompheniramine maleate and imipramine, as well as in combination with sympathomimetics. The calculated efficacy of antimuscarinics alone or in combination with sympathomimetics is 22% and 39%, respectively [211]. Combination therapy appears to be more effective, although statistical analysis is not yet possible due to the small sample sizes.

6.6.3.2 Management of infertility

Infertility has been the major concern of patients with retrograde ejaculation. Beyond standard sperm-retrieval techniques, such as testicular sperm aspiration/extraction (TESA/TESE), three different methods of sperm acquisition have been identified for managing infertility in patients with retrograde ejaculation. These include: i) centrifugation and resuspension of post-ejaculatory urine specimens; ii) the Hotchkiss (or modified Hotchkiss) technique; and, iii) ejaculation on a full bladder.

1. *Centrifugation and resuspension.* In order to improve the ambient conditions for the sperm, the patient is asked to increase their fluid intake or take sodium bicarbonate to dilute or alkalise the urine, respectively. Afterwards, a post-orgasmic urine sample is collected by introducing a catheter or spontaneous voiding. This sample is then centrifuged and suspended in a medium. The types of suspension fluids are heterogeneous and can include bovine serum albumin, human serum albumin, Earle's/Hank's balanced salt solution and the patient's urine. The resultant modified sperm mixture can then be used in assisted reproductive techniques. A systematic review of studies in couples in which the male partner had retrograde ejaculation found a 15% pregnancy rate per cycle (0-100%) [211].
2. *Hotchkiss method.* The Hotchkiss method involves emptying the bladder prior to ejaculation, using a catheter, and then washing out and instilling a small quantity of Lactated Ringers to improve the ambient condition of the bladder. The patient then ejaculates, and semen is retrieved by catheterisation or voiding [779]. Modified Hotchkiss methods involve variance in the instillation medium. Pregnancy rates were 24% per cycle (0-100%) [211].
3. *Ejaculation on a full bladder.* The patient is encouraged to ejaculate on a full bladder and semen is suspended in Baker's Buffer. The pregnancy rate in the two studies, which included only five patients, have described results using this technique [780, 781].

6.7 Anorgasmia

6.7.1 ***Definition and classification***

Anorgasmia is the perceived absence of orgasm and can give rise to anejaculation. Regardless of the presence of ejaculation, anorgasmia can be a lifelong (primary) or acquired (secondary) disorder [208].

6.7.2 ***Pathophysiology and risk factors***

Primary anorgasmia starts from a man's first sexual intercourse and lasts throughout his life, while secondary anorgasmia patients should have a normal period before the problem starts [782]. Substance abuse, obesity and some non-specific psychological aspects, such as anxiety and fear, are considered risk factors for anorgasmia. Only a few studies have described anorgasmia alone and generally, it has been considered a symptom linked to ejaculatory disorders, especially with DE, and therefore, they are believed to share the same risk factors. However, psychological factors are for 90% of anorgasmia problems [783]. The causes of delayed orgasm and anorgasmia are shown in Table 15 [782].

Table 15: Causes of delayed orgasm and anorgasmia [782]

Endocrine	Testosterone deficiency Hypothyroidism
Medications	Antidepressants Antipsychotics Opioids
Psychosexual causes	
Hyperstimulation	
Penile sensation loss	

6.7.3 ***Disease management***

The psychological/behavioural strategies for anorgasmia are similar to those for DE. The patient and his partner should be examined physically and psychosexually in detail, including determining the onset of anorgasmia, medication and disease history, penile sensitivity and psychological issues. Adjunctive laboratory tests can also be used to rule out organic causes, such as testosterone, prolactin and TSH levels. Patients who have loss of penile sensitivity require further investigations [782].

6.7.3.1 Psychological/behavioural strategies

Lifestyle changes can be recommended to affected individuals, including changing masturbation style, taking steps to improve intimacy, and decreasing alcohol consumption. Several psychotherapy techniques or their combinations have been offered, including alterations in arousal methods, reduction of sexual anxiety, role-playing an exaggerated orgasm and increased genital stimulation [744, 784]. However, it is difficult to determine the success rates from the literature.

6.7.3.2 Pharmacotherapy

Several drugs have been reported to reverse anorgasmia, including cyproheptadine, yohimbine, buspirone, amantadine and oxytocin [785-790]. However, these reports are generally from case-cohort studies and drugs have limited efficacy and significant adverse effect profiles. Therefore, current evidence is not strong enough to recommend drugs to treat anorgasmia.

6.7.3.3 Management of infertility

If patients fail the treatment methods mentioned above, penile vibratory stimulation, electro-ejaculation or TESE are options for sperm retrieval in anorgasmia cases [782].

6.8 Haemospermia

6.8.1 ***Definition and classification***

Haemospermia is defined as the appearance of blood in the ejaculate. Although it is often regarded as a symptom of minor significance, blood in the ejaculate causes anxiety in many men and may indicate underlying pathology [231].

6.8.2 ***Pathophysiology and risk factors***

Several causes of haemospermia have been acknowledged and can be classified into the following sub-categories; idiopathic, congenital malformations, inflammatory conditions, obstruction, malignancies, vascular abnormalities, iatrogenic/trauma and systemic causes (Table 16) [791].

Table 16: Pathology associated with haemospermia [791-794]

Category	Causes
Congenital	Seminal vesicle (SV) or ejaculatory duct cysts
Inflammatory	Urethritis, prostatitis, epididymitis, tuberculosis, CMV, HIV, Schistosomiasis, hydatid, condyloma of urethra and meatus, urinary tract infections
Obstruction	Prostatic, SV and ejaculatory duct calculi, post-inflammatory, seminal vesicle diverticula/cyst, urethral stricture, utricle cyst, BPH
Tumours	Prostate, bladder, SV, urethra, testis, epididymis, melanoma

Vascular	Prostatic varices, prostatic telangiectasia, haemangioma, posterior urethral veins, excessive sex or masturbation
Trauma/iatrogenic	Perineum, testis, instrumentation, post-haemorrhoid injection, prostate biopsy, vaso-venous fistula
Systemic	Hypertension, haemophilia, purpura, scurvy, bleeding disorders, chronic liver disease, renovascular disease, leukaemia, lymphoma, cirrhosis, amyloidosis
Idiopathic	-

The risk of any malignancy in patients presenting with haemospermia is approximately 3.5% (0-13.1%) [793, 795]. In a study in which 342 patients with haemospermia were included, the most relevant aetiology for haemospermia was inflammation/infection (49.4%) while genitourinary cancers (i.e., prostate and testis) only accounted for 3.2% of the cases [796].

*6.8.3 **Investigations***

As with other clinical conditions, a systematic clinical history and assessment is undertaken to help identify the cause of haemospermia. Although the differential diagnosis is extensive, most cases are caused by infections or other inflammatory processes [231].

The basic examination of haemospermia should start with a thorough symptom-specific and systemic clinical history. The first step is to understand if the patient has true haemospermia. Pseudo-haemospermia may occur as a consequence of haematuria or even suction of a partner's blood into the urethra during copulation [754, 797, 798]. A sexual history should be taken to identify those whose haemospermia may be a consequence of a STI. Recent foreign travel to areas affected by schistosomiasis or tuberculosis should also be considered. The possibility of co-existing systemic diseases such as hypertension, liver disease and coagulopathy should be investigated along with systemic features of malignancy such as weight loss, loss of appetite or bone pain. Examination of the patient should also include measurement of blood pressure, as there have been several case reports suggesting an association between uncontrolled hypertension and haemospermia [799, 800].

Most authors who propose an investigative baseline agree on the initial diagnostic tests, but there is no consensus in this regard [791, 792, 795, 797]. Urinalysis should be performed along with sending the urine for culture and sensitivity testing, as well as microscopy. If tuberculosis or schistosomiasis is the suspected cause, the semen or prostatic secretions should be sent for analysis. A full sexually-transmitted disease screen, including first-void urine as well as serum and genitourinary samples, should be tested for *Chlamydia, Ureaplasma* and Herpes Simplex virus. Using this strategy, it may be possible to find an infectious agent among cases that would have been labelled as idiopathic haemospermia [801].

Serum PSA should be taken in men aged > 40 years who have been appropriately counselled [232]. Blood work, including a full blood count, liver function tests, and a clotting screen should be taken to identify systemic diseases. The question of whether further investigation is warranted depends on clinician judgment, patient age and an assessment of risk factors [791]. Digital rectal examination should also be performed, and the meatus re-examined after DRE for bloody discharge [802]. Detection of a palpable nodule in the prostate is important because an association between haemospermia and PCa has been postulated, although not completely proven.

Magnetic resonance imaging (MRI) is being increasingly used as a definitive means to investigate haemospermia. The multiplanar ability of MRI to accurately represent structural changes in the prostate, seminal vesicles, ampulla of vas deferens, and ejaculatory ducts has enabled the technique to be particularly useful in determining the origin of midline or paramedian prostatic cysts and in determining optimal surgical management [803]. The addition of an endorectal coil can improve diagnostic accuracy for identifying the site and possible causes of haemorrhage [804].

Cystoscopy has been included in most suggested investigative protocols in patients with high-risk features (patients who are refractory to conservative treatment and who have persistent haemospermia). It can provide valuable information as it allows direct visualisation of the main structures in the urinary tract that can be attributed to causes of haemospermia, such as polyps, urethritis, prostatic cysts, foreign bodies, calcifications and vascular abnormalities [805, 806].

With the advancement of optics, the ability to create ureteroscopes of diameters small enough to allow insertion into the ejaculatory duct and seminal vesicles has been made possible [806, 807]. In a prospective study, 106 patients with prolonged haemospermia underwent transrectal US and seminal vesiculoscopy. With both methods combined, the diagnosis was made in 87.7% of patients. When compared head-to-head, the diagnostic yield for TRUS vs. seminal vesiculoscopy was 45.3% and 74.5%, respectively ($P < 0.001$) [808].

Melanospermia is a consequence of malignant melanoma involving the genitourinary tract and is a rare condition that has been described in two case reports [809, 810]. Chromatography of the semen sample can be used to distinguish the two by identifying the presence of melanin if needed.

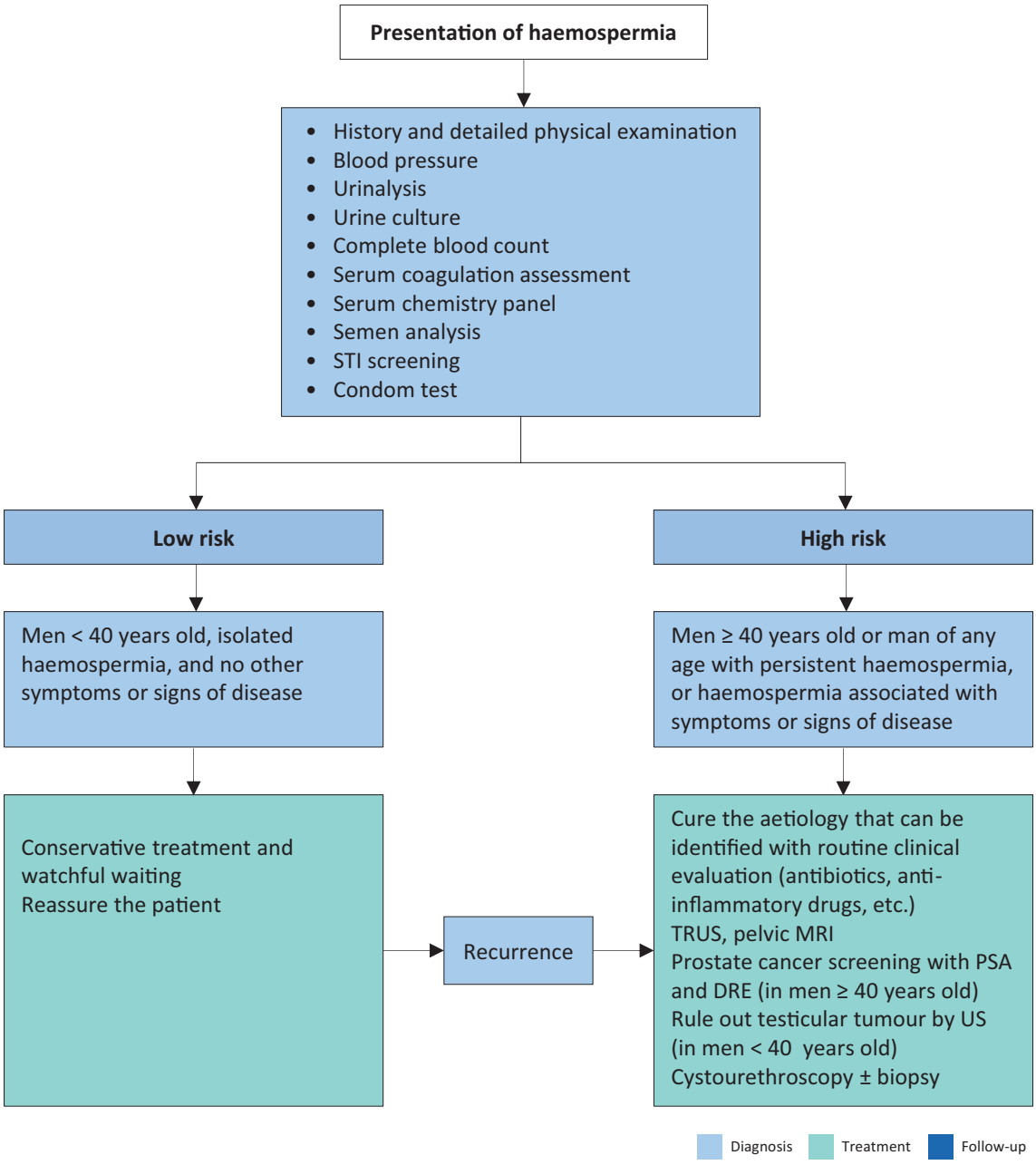
*6.8.4 **Disease management***

Conservative management is generally the primary treatment option when the patients are aged < 40 years and have a single episode of haemospermia. The primary goal of treatment is to exclude malignant conditions like prostate and bladder cancer and treat any other underlying cause. If no pathology is found, then the patient can be reassured [231, 791].

Middle-aged patients with recurrent haemospermia warrant more aggressive intervention. Appropriate antibiotic therapy should be given to patients who have urogenital infections or STIs. Urethral or prostate varices or angiodyplastic vessels can be fulgurated, whereas cysts, either of the seminal vesicles or prostatic urethra, can be aspirated transrectally [231]. Ejaculatory duct obstruction is managed by transurethral incision at the duct opening [811, 812]. Systemic conditions should be treated appropriately [795, 798, 813, 814].

Defining a management algorithm for haemospermia is based on the patient's age and degree of haemospermia. Patients often find blood in the ejaculate alarming, and investigations should be aimed at excluding a serious, despite infrequent, underlying cause (e.g., cancer), while at the same time preventing over-investigation and alleviating patient anxiety. The literature describes a multitude of causes for haemospermia, although many of these are not commonly found after investigation. However, men may be stratified into higher-risk groups according to several factors including: age > 40 years, recurrent or persistent haemospermia, the actual risk for PCa (e.g., positive family history), and concurrent haematuria. Based on the literature, a management algorithm is proposed (Figure 8) [795, 798, 813, 814].

Figure 8: Management algorithm for haemospermia [795, 798, 813, 814]



STI = Sexually transmitted infections; PSA = Prostate specific antigen; DRE = Digital rectal examination; US = Ultrasonography; TRUS = Transrectal ultrasonography; MRI = Magnetic resonance imaging.

6.8.5 *Summary of evidence and recommendations for the investigation and management of haemospermia*

Summary of evidence	LE
While haemospermia has traditionally been attributed to benign causes, it is a potential indicator warranting thorough diagnostic evaluation and, if necessary, targeted treatment.	3
The principal objective of treatment is to rule out malignancies, while addressing any other underlying causes as well.	3

Recommendations	Strength rating
Perform a full medical and sexual history with detailed physical examination.	Strong
Use a risk-stratification system to manage the disease systematically.	Weak

7. LOW SEXUAL DESIRE AND MALE HYPOACTIVE SEXUAL DESIRE DISORDER

7.1 Definition, classification and epidemiology

It has always been a challenge to define sexual desire properly because it has a complicated nature and it can be conceptualised in many different ways. According to the International Classification of Diseases 10th edition (ICD-10), lack or loss of sexual desire should be the principal problem and not other sexual problems accompanying it such as ED [815]. In the DSM-V, male hypoactive sexual desire disorder (HSDD) is defined as "the persistent or recurrent deficiency (or absence) of sexual or erotic thoughts or fantasies and desire for sexual activity". The clinician makes the judgment of deficiency, taking into account factors that affect sexual functioning, such as age and general and socio-cultural contexts of the individual's life [207]. According to the fourth International Consultation on Sexual Medicine (ICSM), the definition of male HSDD was proposed as a "persistent or recurrent deficiency or absence of sexual or erotic thoughts or fantasies and desire for sexual activity (clinical principle)" [816]. Although the exact prevalence of low sexual desire (LSD) is unknown, a prevalence of 4.7% was reported in a survey of a population-based sample of middle-aged German men (n = 12,646) [817].

7.2 Pathophysiology and risk factors

Several aetiological factors are considered to contribute to the pathophysiology of LSD. Levine proposed three components of sexual desire drive (biological), motivation (psychological) and wish (cultural) [818]. However, it is believed that both in the surveys and clinical practice those three components are usually found interwoven [819].

*7.2.1 **Psychological aspects***

The endorsement of negative thoughts during sexual intercourse (i.e., concerns about erection, lack of erotic thoughts, and restrictive attitudes toward sexuality) predicts LSD in men [820, 821]. Furthermore, feeling shame during sexual intercourse, because of negative sexual thoughts (e.g., concern about achieving an erection), characterises men with LSD as opposed to women with the same condition [822]. Psychopathological symptoms stemming from a crisis context negatively impacted male sexual desire [332], as well. In addition, dyadic male sexual desire was best accounted for by sexual satisfaction [823]. It is worth noting that, despite LSD being less common in men than in women [816], it is the most frequent complaint in couples' therapy [824]. Therefore, the role of relationship factors must be addressed. In addition, anxiety proneness has been associated with LSD in men and is expected to shift men's attention from erotic cues to worrying thoughts, thereby decreasing sexual desire [825]. Finally, it is worth noting that current approaches focus on sexual desire discrepancies between partners; the focus on discrepancies rather than on the partner who presents low desire not only reduces stigma, but also provides new opportunities for managing desire in the relationship context [826].

*7.2.2 **Biological aspects***

Testosterone seems to be essential for a man's sexual desire; however, sexual desire does not directly relate to the circulating level of testosterone, especially in older men [827]. The biological and psychological components that take place in the pathophysiology of LSD are shown in Table 22 [819, 828]. In addition to these factors, there is some speculation about the role of the thyroid and oxytocin hormones [555, 829].

Table 22: Common causes of low sexual desire in men [819, 828]

Androgen deficiency
Hyperprolactinaemia
Anger and anxiety
Depression
Relationship conflict
Stroke
Antidepressant therapy
Epilepsy
Post-traumatic stress syndrome

Renal failure
Coronary disease and heart failure
Ageing
HIV infection
Body-building and eating disorders
Erectile dysfunction
Prostatitis/chronic pelvic pain syndrome

*7.2.3 **Risk factors***

In an international survey aimed at estimating the prevalence and correlates of sexual problems in 13,882 women and 13,618 men from 29 countries (Global Study of Sexual Attitudes and Behaviours), risk factors for male LSD were age 60-69 and 70-80 years, poor overall health, vascular diseases, being a current smoker, belief that ageing reduces sex, divorce in the past 3 years, financial problems in the last 3 years, major depression, being worried about the future of a relationship and less than one sexual relation in a week [205]. In a recent study that determined the factors associated with LSD in a large sample of middle-aged German men, PE, ED, and lower urinary tract symptoms were associated with LSD [817]. In contrast, men having more than two children, higher frequency of solo masturbation, perceived importance of sexuality, and higher sexual self-esteem were less likely to have LSD [817].

7.3 Diagnostic work-up

*7.3.1 **Assessment questionnaires***

Sexual Desire Inventory (SDI) evaluates different components influencing the development and expression of sexual desire [830]. This self-administered questionnaire consists of 14 questions that weigh the strength, frequency, and significance of an individual's desire for sexual activity with others and by themselves. The SDI suggests that desire can be split into two categories: dyadic and solitary desire. While dyadic desire refers to "interest in or a wish to engage in sexual activity with another person and desire for sharing and intimacy with another", solitary desire refers to "an interest in engaging in sexual behaviour by oneself and may involve a wish to refrain from intimacy and sharing with others" [830].

*7.3.2 **Physical examination and investigations***

Similar to other forms of sexual dysfunctions, a thorough medical and sexual history must be obtained from men who complain of LSD. The depressive symptoms of the patients must be assessed [831] and relationship problems (e.g., conflict with the sexual partner) must be questioned. In the presence of accompanying symptoms suggestive of endocrinological problems, circulating total testosterone [832], prolactin [833] and thyroid hormones [555] levels can be evaluated.

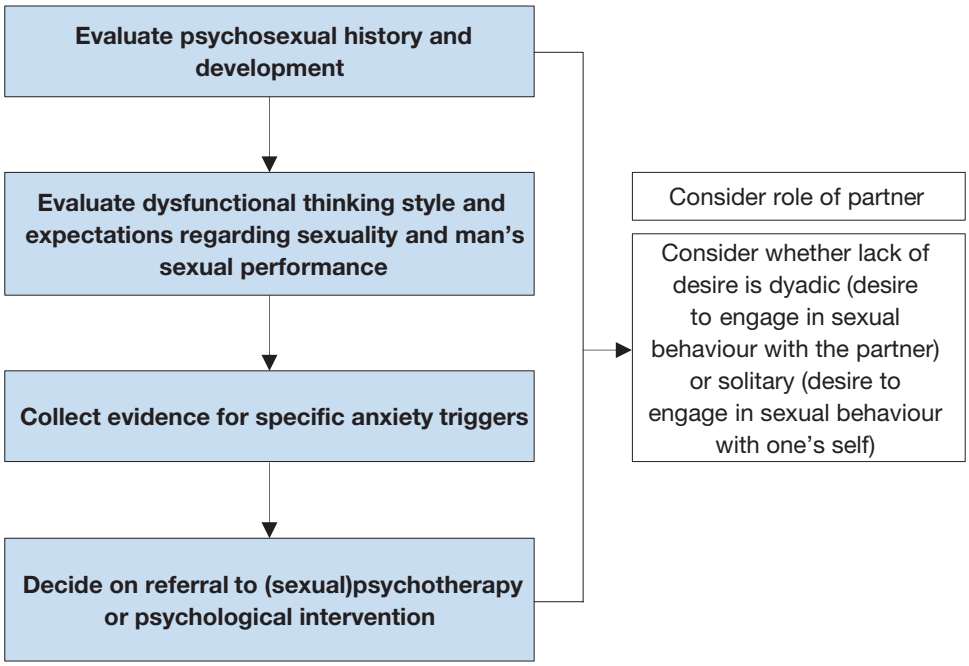
7.4 Disease management

Treatment of LSD should be tailored according to the underlying aetiology.

*7.4.1 **Psychological intervention***

Data on the efficacy of psychological interventions for LSD are scarce. Accordingly, recommendations must be interpreted with caution. Psychological interventions with a focus on cognitive and behavioural strategies may be beneficial for LSD in men [336, 834] (Figure 9). Mindfulness treatments may be a strong candidate, as well [834]. Since both members of a couple may experience age-related changes concurrently and interdependently, it could be helpful to address the sexual health needs of the ageing couple (including LSD) as a whole rather than treating the individual patient [835]. Indeed, psychologists are putting more emphasis on the concept of sexual desire discrepancy. Sexual desire discrepancy is often found in couples or partners, and mirror a natural part of life and partners' dynamics. Clinical approaches based on this lens are less stigmatising as they consider the normal variations in sexual desire that occur throughout the lifespan. This intervention option targets couples distressed by sexual desire discrepancies rather than a single individual targeted as the one presenting low sexual desire [826].

Figure 9: Flow-diagram of psychological evaluation of patients with low sexual desire



7.4.2 ***Pharmacotherapy***

Low sexual desire secondary to low testosterone levels can be treated with different formulations of testosterone. The favourable effect of testosterone therapy on sexual motivation and the presence of sexual thoughts was shown in a meta-analysis [832]. The aim of treatment should be to reach the physiological range of testosterone (see Section 3.3).

Hyperprolactinaemia can also cause LSD and one of the most relevant aetiological factors is prolactin-secreting pituitary adenomas. These adenomas can be easily diagnosed with an MRI of the pituitary gland and can be treated with dopamine agonist agents [836]. The other accompanying endocrine disorders, such as hypothyroidism, hyperthyroidism and diabetes, should be treated accordingly.

Pharmacotherapy can also be used to treat major depression; however, it should be remembered that antidepressants may negatively affect sexual functioning; therefore, antidepressant compounds with less effect on sexual function should be chosen. Psychotherapy can increase the efficacy of pharmacotherapy, especially for patients whose LSD is due to depression [837].

7.5 Recommendations for the treatment of low sexual desire

Recommendations	Strength rating
Perform the diagnosis and classification of low sexual desire (LSD) based on medical and sexual history, which could include validated questionnaires.	Weak
Include physical examination in the initial assessment of LSD to identify anatomical abnormalities that may be associated with LSD or other sexual dysfunctions, particularly erectile dysfunction.	Weak
Perform laboratory tests to rule out endocrine disorders.	Strong
Modulate chronic therapies which can negatively impact toward sexual desire.	Weak
Provide testosterone therapy if LSD is associated with signs and symptoms of testosterone deficiency.	Strong

8. PENILE CURVATURE

8.1 Congenital penile curvature

8.1.1 Epidemiology/aetiology/pathophysiology

Congenital penile curvature (CPC) is a rare condition, with a reported incidence of < 1% [838], although some studies have reported higher prevalence rates of 4-10%, in the absence of hypospadias [839]. Congenital penile curvature results from disproportionate development of the tunica albuginea of the corporal bodies and is not associated with urethral malformation. In most cases, the curvature is ventral, but it can also be lateral or, more rarely, dorsal [840].

8.1.2 Diagnostic evaluation

Taking a medical and sexual history is usually sufficient to establish a diagnosis of CPC. Patients usually present after reaching puberty as the curvature becomes more apparent with erections and sexual activity. The more severe curvatures can make intercourse difficult or impossible. Physical examination and photographic documentation during erection (preferably after intracavernous injection [ICI] of vasoactive drugs) are both mandatory to document the curvature and exclude other pathologies [840].

8.1.3 Disease management

Surgery is the definitive treatment for this disorder and can be deferred until after puberty. However, a survey has suggested that men with untreated ventral penile curvature report more dissatisfaction with penile appearance, increased difficulty with intercourse, and psychological problems; supporting surgical correction of CPC in childhood, although this should be discouraged as penile growth will not have maximised [841]. Surgical treatments for CPC generally share the same principles as in PD. Plication techniques (Nesbit, 16-dot, Yachia, Essed-Schröeder, and others) with or without neurovascular bundle elevation (medial/lateral) and complete penile degloving, have been described [842-851]. Other approaches are based on corporal body de-rotation with different technical refinements that enable correction of a ventral curvature, with reported minimal narrowing and shortening [852-855]. There are no direct comparative studies; therefore, no single technique can be recommended for surgical correction.

8.1.4 Summary of evidence and recommendation for diagnosis and treatment of congenital penile curvature

Summary of evidence	LE
Medical and sexual history are usually sufficient to establish a diagnosis of CPC. Physical examination and photographic documentation during erection (preferably after ICI of vasoactive drugs) are mandatory to document the curvature.	3
Surgery is the only treatment option for CPC, which should be deferred until after puberty and performed at any time in adult life in individuals with significant functional impairment during intercourse.	3

8.1.5 Recommendation for the treatment of congenital penile curvature

Recommendation	Strength rating
Use the Nesbit procedure or plication techniques with or without neurovascular bundle dissection (medial/lateral) for satisfactory curvature correction.	Strong

8.2 Peyronie's Disease

(A discussion on the Aetiology, Risk factors and Pathophysiology of PD can be found in Appendix 4, online supplementary evidence.)

8.2.1 Epidemiology

Epidemiological data on PD are limited. Prevalence rates of 0.4-20.3% have been reported, with a higher prevalence in patients with ED and diabetes [856-864]. A recent survey has indicated that the prevalence of definitive and probable cases of PD in the USA is 0.7% and 11%, respectively, suggesting that PD is an under-diagnosed condition [865]. Peyronie's disease often occurs in older men with a typical age of onset of 50-60 years. However, PD also occurs in younger men (< 40 years), with a reported prevalence of 1.5-16.9% [860, 866, 867].

*8.2.2 **Diagnostic evaluation***

The initial evaluation aims to obtain information on the presenting symptoms and their duration (e.g., pain on erection, palpable nodules, deformity, length and girth and erectile function). It is important to obtain information on the distress caused by the symptoms and the potential risk factors for ED and PD. A disease-specific questionnaire (Peyronie's disease questionnaire [PDQ]) has been developed for use in clinical practice and trials. The Peyronie's disease questionnaire measures three domains, including psychological and physical symptoms, penile pain and symptom bother [868].

Clinicians should take a focused history to distinguish between active and stable disease, as this will influence medical treatment and the timing of surgery. Patients who are still likely to have active disease are those with a shorter symptom duration, pain on erection, or a recent change in penile deformity. Resolution of pain and stability of the curvature for at least three months are accepted criteria of disease stabilisation as well as patients' referral for specific medical therapy [869, 870] or surgical intervention, if indicated [871].

The examination should start with a focused genital assessment that is extended to the hands and feet for detecting possible Dupuytren's contracture or Ledderhose scarring of the plantar fascia [872]. A penile examination is performed to assess the presence of a palpable nodule or plaque. There is no correlation between plaque size and degree of curvature [873]. Measurement of the stretched or erect penile length is important because it may have an impact on the subsequent treatment decisions and potential medico-legal implications [874-876].

An objective assessment of penile curvature with an erection is mandatory. This can be obtained by several approaches, including home (self) photography of a natural erection (preferably), using a vacuum-assisted erection test or an ICI using vasoactive agents. However, it has been suggested that the ICI method is superior, as it can induce an erection similar to or better than that which the patient would experience when sexually aroused [877-879]. Computed tomography and MRI have a limited role in the diagnosis of the curvature and are not recommended on a routine basis. Erectile function can be assessed using validated instruments such as the IIEF although this has not been validated in PD patients [880]. Erectile dysfunction is common in patients with PD (30-70.6%) [881, 882]. The presence of ED and psychological factors may also have a profound impact on the chosen treatment strategy [883]. Ultrasound measurement of plaque size is not accurate but may be helpful to assess the presence of the plaque and its calcification and location [884, 885]. Doppler US may be used for the assessment of penile haemodynamics and ED aetiology [882]. In particular to assess penile arterial inflow in the context of the interventional modality to be undertaken (eg plaque incision and grafting) to exclude arteriogenic ED.

8.2.2.1 Summary of evidence and recommendations for diagnosis of Peyronie's disease

Summary of evidence	**LE**
Ultrasound measurement of plaque size is inaccurate and operator-dependent.	3
Doppler US may be used to assess penile haemodynamic and vascular anatomy.	2a
Intracavernous injection method is superior to other methods in providing an objective assessment of penile curvature with an erection.	4

Recommendations	**Strength rating**
Take a medical and sexual history of patients with Peyronie's disease (PD), including duration of the disease, pain on erection, penile deformity, difficulty in vaginal/anal intromission due to the deformity and erectile dysfunction (ED).	Strong
Perform a physical examination, including assessment of palpable plaques, stretched or erect penile length, degree of curvature (self-photography, vacuum-assisted erection test or pharmacological-induced erection) and any other related diseases (e.g., Dupuytren's contracture, Ledderhose disease) in patients with PD.	Strong
Use the intracavernous injection (IC) method in the diagnostic work-up of PD to provide an objective assessment of penile curvature with an erection.	Weak
Use the PD specific questionnaire especially in clinical trials, but routine use in daily clinical practice is not mandatory.	Weak

Do not use ultrasound (US), computed tomography or magnetic resonance imaging to assess plaque size and deformity in routine clinical practice.	Weak
Use penile Doppler US in the case of diagnostic evaluation of ED, to evaluate penile haemodynamic and vascular anatomy, and to assess location and calcification of plaques, especially prior to surgery.	Weak

*8.2.3 **Disease management***

8.2.3.1 Conservative treatment

Conservative treatment of PD is primarily focused on patients in the early stage of the disease as an adjunct treatment to relieve pain and prevent disease progression or if the patient declines other treatment options during the active phase [871, 872]. Several options have been suggested, including oral pharmacotherapy, intralesional injection therapy, shockwave therapy (SWT) and other topical treatments (Table 16).

The results of the studies on conservative treatment for PD are often contradictory, making it difficult to provide recommendations in everyday, real-life settings [886]. The Guidelines do not recommend the use of oral treatments for PD including pentoxifylline, vitamin E, tamoxifen, procarbazine, potassium para-aminobenzoate (potaba), omega-3 fatty acids or a combination of vitamin E and L-carnitine because of their lack of proven efficacy [871, 887-889]. Studies of these treatments have numerous methodological problems including their uncontrolled nature, the limited number of patients treated, the short-term follow-up and the different outcome measures used [890, 891]. Even in the absence of adverse events, treatment with these agents may delay the use of other more efficacious treatments.

Table 16: Conservative treatments for PD

Oral treatments
Nonsteroidal anti-inflammatory drugs (NSAIDs)
Phosphodiesterase type 5 inhibitors (PDE5Is)
Intralesional treatments
Verapamil
Nicardipine
Clostridium collagenase
Interferon α2B
Hyaluronic acid
Botulinum toxin
Topical treatments
H-100 gel
Other
Traction devices
Multimodal treatment
Extracorporeal shockwave treatment
Vacuum Erection Device

8.2.3.1.1 Oral treatment

Phosphodiesterase type 5 inhibitors

Phosphodiesterase type 5 inhibitors were first suggested as a treatment for PD in 2003 to reduce collagen deposition and increase apoptosis through the inhibition of transforming growth factor (TGF)-b1 [892-894]. The results of a retrospective study of 65 men indicated that treatment with tadalafil was helpful in decreasing helped decrease curvature and remodel septal scars when compared to controls [895]. Another study concluded that sildenafil was able to improve erectile function and pain in PD patients. Thirty-nine patients with PD were divided into two groups receiving vitamin E (400 IU) or sildenafil 50 mg for twelve weeks with significantly better outcomes in pain and mean IIEF scores were seen in the sildenafil group [896]. Findings from a observational retrospective study including patients in the acute phase of PD and ED who had been treated with Tadalafil 5 mg once daily compared to patients with comparable baseline parameters who decided not to take the daily compound (i.e., 108 intervention vs. 83 controls) showed that treated men had lower curvature progression rates at 12 weeks (25.9% vs. 39.7%, p = 0.042) [897]. Similarly, mean SHIM score and PDQ-Overall and PDQ-Penile Pain scores significantly improved in the intervention group ($p < 0.001$).

Nonsteroidal anti-inflammatory drugs
Nonsteroidal anti-inflammatory drugs (NSAIDs) may be offered to patients in active-phase PD to ameliorate penile pain. Pain levels should be periodically reassessed whilst monitoring treatment efficacy.

8.2.3.1.2 Intralesional treatment
Injection of pharmacologically active agents directly into penile plaques represents another treatment option. It allows a localised delivery of a pharmacological 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.

Calcium channel antagonists: verapamil and nicardipine
The rationale for intralesional use of channel antagonists in patients with PD is based on *in vitro* research [898, 899]. Due to the use of different dosing schedules and the contradictory results obtained in published studies, the evidence is not strong enough to support the clinical use of injected channel blockers verapamil and nicardipine and the results do not demonstrate a meaningful improvement in penile curvature compared to placebo [900-905]. In fact, most of the studies did not perform direct statistical comparisons between these groups.

Collagenase of Clostridium histolyticum
Collagenase of *Clostridium histolyticum* (CCH) is a chromatographically purified bacterial enzyme that selectively targets collagen, the primary component of the PD plaque [906-909]. Intralesional injection of CCH has been used in the treatment of PD since 1985. In 2014 the EMA approved CCH for the non-surgical treatment of the stable phase of PD in men with palpable dorsal plaques in whom abnormal curvature of 30-90o and non-ventrally located plaques are present. It should be administered by a healthcare professional who is experienced and properly trained in the administration of CCH treatment for PD [910, 911]. However, CCH has been officially withdrawn from the European market by its manufacturer. Despite this the evidence and recommendations for CCH have been maintained by the Guidelines for completeness.

The original treatment protocol in all studies consists of two injections of 0.58 mg of CCH 24-72 hours apart every six weeks for up to four cycles. Data from IMPRESS (Investigation for Maximal Peyronie´s Reduction Efficacy and Safety Studies) II and II studies [976], as well as post-approval trials [912], which demonstrated the efficacy and safety of this treatment, are summarised in Table 8.2 online Appendix 5.

The average improvement in curvature was 34% compared to 18.2% in the placebo group. Three adverse events of corporeal rupture were surgically repaired. The greatest chance of curvature improvement was for curvatures between 30° and 60°, longer duration of disease, IIEF > 17, and no calcification [870]. An 18.2% improvement from baseline in the placebo arm was also observed. These findings raise questions regarding the proposed role of plaque injection and penile modelling, regardless of the medication, in improving outcomes in men with PD as the placebo or modelling arm resulted in relatively high curvature reduction compared to the treatment arm.

The conclusion of the IMPRESS I and II studies is that CCH improves PD both physically and psychologically [913]. A *post hoc* meta-analysis of the IMPRESS studies demonstrated better results in patients with curvatures < 60º, > 2 years of onset, no calcification in the plaque and good erectile function [912].

Thereafter, a modified short protocol consisting of administration of a single (0.9 mg, one vial) injection per cycle distributed along three lines around the point of maximum curvature up to three cycles, separated by 4-weekly intervals, has been proposed and rapidly popularised replacing physician modelling with a multi-modal approach through penile stretching, modelling and VED at home [914]. The results from this modified protocol were comparable to the results of the IMPRESS trials and appeared to decrease the cost and duration of treatment, although these studies were non-randomised. However, these results were further explored in a prospective non-randomised multi-centre study [982]. In another large single-arm multi-centre clinical study using the shortened protocol, longer PD duration, greater baseline PC and basal and dorsal plaque location were identified as clinically significant predictors of treatment success [915]. Accordingly, a nomogram developed to predict treatment success after CCH for PD showed that patients with longer PD duration, greater baseline penile curvature and basal plaque location had a greater chance of treatment success [915]; however, these findings need to be externally validated.

Regarding safety concerns, most PD patients treated with CCH experienced at least one mild or moderate adverse event localised to the penis (penile haematoma (50.2%), penile pain (33.5%), penile swelling (28.9%) and injection site pain (24.1%), which resolved spontaneously within 14 days of injection [916]. The adverse reaction

profile was similar after each injection, regardless of the number of injections administered. Serious treatment-emergent adverse events (TEAEs) (0.9%) included penile haematoma and corporeal rupture that require surgical treatment. According to IMPRESS data and the shortened protocol, to prevent serious TEAEs men should be advised to avoid sexual intercourse in the four weeks following injection. Recent preliminary data suggest that treatment in the acute phase of the disease is effective and safe [880, 917-921].

In conclusion, CCH is a safe and established treatment for stable-phase disease wit more recent evidence suggesting that CCH also has a role in affecting the progression of active-phase disease. It should also be noted that there is a large effect of traction or modelling in controlled studies, whilst studies reporting on modified protocols have small numbers of patients and are largely uncontrolled. Therefore, patients should be counselled fully on the efficacy of collagenase and the high cost of treatment.

It has been suggested that those patients with severe curvature may also benefit from CCH injections because of a potential downgrading of the penile curvature: a decrease in curvature may allow for a penile plication procedure instead of a plaque incision and grafting procedure, therefore avoiding the more negative impact on erectile function from plaque incision and grafting. However, further studies are required to validate these initial findings [880, 921].

Interferon α-2b

Intralesional injections (5x10^6 units of IFN-α2b in 10 mL saline every 2 weeks over 12 weeks for a total of six injections) significantly improved penile curvature, plaque size and density, and pain compared to placebo. Additionally, penile blood flow parameters are benefited by IFN-α2b [911, 922, 923]. Regardless of plaque location, IFN-α2b is an effective treatment option. Treatment with IFN-α2b provides a > 20% reduction in curvature in most men with PD, independent of plaque location [924]. Given the mild adverse effects, which include sinusitis and flu-like symptoms, which can be effectively treated with NSAIDs before IFN-α2b injection, and the moderate strength of data available, IFN-α2b is currently recommended for treatment of stable-phase PD.

Steroids, hyaluronic acid and botulinum toxin (botox)

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 [925]. Adverse effects include tissue atrophy, thinning of the skin and immunosuppression [926]. The effect of hyaluronic acid treatment in patients with PD was investigated in a non-randomised study; intralesional injection of hyaluronic acid was compared to intralesional verapamil in acute phase PD and significant improvement of pain, curvature and IIEF-15 were observed [927]. In an RCT, oral administration of hyaluronic acid combined with intralesional injection was found to be superior to intralesional injection only and an improvement of 7.8±3.9 degrees in curvature and reduction in plaque size of 3.0 mm was observed [928]. There is only a single study evaluating intralesional botox injections in men with PD; therefore, there is insufficient evidence to support this treatment in clinical practice [929].

Platelet Rich Plasma (PRP)

Few studies in humans have evaluated the effect of PRP on penile curvature, plaque size, PDQ and IIEF [930-935]. The effect of PRP in patients with PD remains to be proven and should be considered experimental. An ongoing phase 2b randomized placebo-controlled crossover trial has enrolled 25 patients with a planned target of 80 men with PD: first ongoing data on nine patients in the treatment group vs eight in the placebo group showed no difference in curvature at three months in comparison to baseline [936].

8.2.3.1.3 Topical treatments

Topical verapamil and H-100 Gel

There is insufficient evidence that topical treatments (verapamil and H-100 Gel) applied to the penile shaft, with or without the use of iontophoresis (now known as transdermal electromotive drug administration), result in adequate levels of the active compound within the tunica albuginea [937-940].

8.2.3.1.4 Other treatments

Extracorporeal shockwave treatment

The mechanism of action involved in ESWT for PD is still unclear.

Four RCTs and one meta-analysis [941-945] assessed the efficacy of ESWT for PD. Three were sham-controlled trials while one compared ESWT with the combination of ESWT and PDE5I (tadalafil) [946].

All trials showed positive findings in terms of pain relief, but no effect on penile curvature and plaque size. Inclusion criteria varied widely among studies and further investigation is needed. Therefore, ESWT should not be used as a primary treatment for penile curvature in men with PD. The results are summarised in Table 8.4 online Appendix 5.

Penile traction therapy

In men with PD, potential mechanisms for disease modification with penile traction therapy (PTT) have been proposed, including collagen remodelling via decreased myofibroblast activity and matrix metalloproteinase up-regulation [947, 948].

The stated clinical goals of PTT are to non-surgically reduce curvature, enhance girth, and recover lost length, which are attractive to patients with PD. However, clinical evidence is limited due to the small number of patients included (267 in total), the heterogeneity in the study designs, and the non-standardised inclusion and exclusion criteria which make it impossible to draw any definitive conclusions about this therapy [949-953].

Most of the included patients will need further treatment to ameliorate their curvature for satisfactory sexual intercourse. Moreover, the effect of PTT in patients with calcified plaques, hourglass or hinge deformities which are, theoretically, less likely to respond to PTT has not been systematically studied. In addition, the treatment can result in discomfort and be inconvenient as the device needs to be used for an extended period (2-8 hours daily), but has been shown to be tolerated by highly-motivated patients. There were no reported serious adverse effects, including skin changes, ulcerations, hypo-aesthesia or diminished rigidity [951, 954].
In conclusion, PTT seems to be effective and safe for patients with PD [955], but there is still lack of evidence to give any definitive recommendation in terms of its use as a monotherapy for PD.

Vacuum erection device

Vacuum erection device (VED) therapy results in dilation of cavernous sinuses, decreased retrograde venous blood flow and increased arterial inflow [956]. Intracorporeal molecular markers are affected by VED application, including decreases in hypoxia-inducible factor-1α, TGF-β1, collagenase, and apoptosis, and increases in endothelial nitric oxide synthase (eNOS) and α-smooth muscle actin, given their role in the pathogenesis of PD [957]. Only two retrospective studies assessed the efficacy of VED therapy in mechanically straightening the penile curvature of PD as monotherapy and further studies are needed [958, 959].

Multimodal treatment

There is some evidence suggesting that a combination of different oral agents can be used for the treatment of the acute phase of PD. However, there does not seem to be a consensus on which drugs to combine or the optimum drug dosage; nor has there been a comparison of different drug combinations.

A long-term study assessing the role of multimodal medical therapy (injectable verapamil associated with antioxidants and local diclofenac) demonstrated that treatment was efficacious to treat PD patients. It concluded that combination therapy reduced pain more effectively than verapamil alone, making this specific combination treatment more effective compared to monotherapy [957]. Furthermore, combination protocols including injectable therapies, such as CCH, have been studied in controlled trials. The addition of adjunctive PTT and VED has been described; however, limited data are available regarding their use [960].

Penile traction therapy has been evaluated as an adjunct therapy to intralesional injections with interferon, verapamil, or CCH [901, 961, 962]. These studies have failed to demonstrate significant improvements in penile length or curvature, except for one subset analysis identifying a 0.4 cm length increase among men using the devices for > 3 hours/day [962]. A meta-analysis demonstrated that men who used PTT as an adjunct to surgery or injection therapy for PD had, on average, an increase in stretched penile length (SPL) of 1 cm compared to men who did not use adjunctive PTT. There was no significant change in curvature between the two groups [963].

Data available on the combined treatment of CCH and the use of VED between injection intervals have shown significant mean improvements in curvature (-17º) and penile length (+0.4 cm) after treatment. However, it is not possible to determine the isolated effect of VED because of a lack of control groups [914, 963].

Also, a combination of PDE5I (sildenafil 25 mg twice daily) after CCH treatment (shortened protocol combined with VED) is superior to CCH alone for improving penile curvature and erectile function [964]. Further studies are necessary to externally validate those findings.

8.2.3.1.5 Summary of evidence and recommendations for conservative treatment of Peyronie's disease

Summary of evidence	LE
Conservative treatment for PD is primarily aimed at treating patients in the early stage of the disease in order to relieve symptoms and prevent progression.	3c
There is no convincing evidence supporting oral treatment with acetyl esters of carnitine, vitamin E, potassium para-aminobenzoate (potaba) and pentoxifylline.	3c
Due to adverse effects, treatment with oral tamoxifen is no longer recommended.	3c
Nonsteroidal anti-inflammatory drugs can be used to treat pain in the acute phase.	4
Contradictory evidence is available for intralesional treatment with calcium channel antagonists: verapamil and nicardipine.	4
Intralesional treatment with Collagenase clostridium histolyticum showed significant decreases in penile curvature, plaque diameter and plaque length in men with stable disease.	1b
Intralesional treatment with interferon may improve penile curvature, plaque size, density, and pain.	2b
Intralesional treatment with steroids hase been shown to have adverse effects, including tissue atrophy, thinning of the skin and immunosuppression.	3c
No high-level evidence is available to support treatment with intralesional hyaluronic acid or botulinum toxin.	3c
Intralesional hyaluronic acid may be used to improve pain, penile curvature and IIEF scores.	2b
A combination of oral and intralesional hyaluronic acid treatment improves penile curvature and plaque size.	1b
There is no evidence that topical treatments applied to the penile shaft result in adequate levels of the active compound within the tunica albuginea.	3c
There is no efficacy data for the use of iontophoresis.	3c
Extracorporeal shockwave treatment may be offered to treat penile pain, but it does not improve penile curvature and plaque size.	2b
Treatment with penile traction therapy alone or in combination with injectable therapy as part of a multimodal approach may reduce penile curvature and increase penile length, although the available studies have considerable limitations.	3c

Recommendation	Strength rating
Offer conservative treatment to patients not fit for surgery or when surgery is not acceptable to the patient.	Strong
Fully counsel patients regarding all available treatment options and outcomes before starting any treatment.	Strong
Do not offer oral treatment with vitamin E, potassium para-aminobenzoate (potaba), tamoxifen, pentoxifylline, colchicine and acetyl esters of carnitine to treat Peyronie's disease (PD).	Strong
Use nonsteroidal anti-inflammatory drugs to treat penile pain in the acute phase of PD.	Strong
Use extracorporeal shockwave treatment (ESWT) to treat penile pain in the acute phase of PD.	Weak
Use phosphodiesterase type 5 inhibitors to treat concomitant erectile dysfunction or if the deformity results in difficulty in penetrative intercourse in order to optimise penetration.	Weak
Offer intralesional therapy with interferon alpha-2b to patients with stable curvature dorsal or lateral > 30^{o} seeking a minimal invasive procedure.	Weak
Offer intralesional therapy with Collagenase *Clostridium Histolyticum* to patients with stable PD and dorsal or lateral curvature > 30^{0}, who request non-surgical treatment, although the placebo effects are high.	Strong
Do not offer intralesional treatment with steroids to reduce penile curvature, plaque size or pain.	Strong

Do not use intralesional platelet-rich plasma or hyaluronic acid, either alone or in combination with oral treatment, to reduce penile curvature, plaque size or pain outside the confines of a clinical trial.	Strong
Do not offer ESWT to improve penile curvature and reduce plaque size.	Strong
Offer penile traction devices and vacuum devices to reduce penile deformity or as part of a multimodal therapy approach, although outcome data is limited.	Weak

8.2.3.2 Surgical treatment

Although conservative treatment for PD may resolve painful erections in most men, only a small percentage experience significant straightening of the penis. The aim of surgery is to correct curvature and allow penetrative intercourse. Surgery is indicated in patients with significant penile deformity and difficulty with intercourse associated with sexual bother. Patients must have a stable disease for three to six months (or more than nine to twelve months after onset of PD) [871, 965, 966]. In addition to this requirement, other situations that may precipitate an indication for surgery, such as failed conservative or medical therapies, extensive penile plaques, or patient preference, when the disease is stable [967, 968].

Before considering reconstructive surgery, it is recommended to document the size and location of penile plaques, the degree of curvature, complex deformities (hinge or hourglass), the penile length and the presence or absence of ED. The potential aims and risks of surgery should be fully discussed with the patient so that he can make an informed decision [966]. Specific issues that should be mentioned during this discussion are: risk of penile shortening; ED, penile numbness; and delayed orgasm, the risk of recurrent curvature, potential for palpation of knots and stitches underneath the skin, potential need for circumcision at the time of surgery, residual curvature and the risk of further penile wasting with shortening procedures [871, 969]. 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 [871]. Patient expectations from surgery must also be included in the pre-operative assessment. The main objective of surgery is to achieve a “functionally straight” penis, and this must be fully understood by the patient to achieve the best possible satisfaction outcomes after surgery [966, 970].

Three major types of reconstruction may be considered for PD: (i) tunical shortening procedures; (ii) tunical lengthening procedures; and, (iii) penile prosthesis implantation, with or without straightening techniques in the presence of concomitant ED and residual curvature [971, 972].

Penile degloving with associated circumcision (as a means of preventing post-operative phimosis) should be considered the standard approach for all types of procedures, although modifications have been described. Only one study has suggested that circumcision is not always necessary (e.g., in cases where the foreskin is normal pre-operatively) [973]. Non-degloving techniques have been described that have been shown to prevent ischaemia and lymphatic complications after subcoronal circumcision [974, 975].

There are no standardised questionnaires for the evaluation of surgical outcomes. Data from well-designed prospective studies are scarce, with low levels of evidence. Data are mainly based on retrospective single-centre studies, typically non-comparative and non-randomised, or expert opinion [871]. Therefore, surgical outcomes must be treated with caution.

8.2.3.2.1 Tunical shortening procedures

Tunical shortening procedures achieve straightening of the penis by shortening the longer, convex side of the penis. For men with good erectile function, adequate penile length, without complex deformities, such as an hourglass or hinge type narrowing abnormalities, and non-severe curvature, a tunical shortening procedure can be considered an appropriate surgical approach. Numerous different techniques have been described, although they can be classified as excisional, incisional and plication techniques. The Nesbit procedure operation is based on an elliptical excision of tunica albuginea opposite to the point of maximum curvature [977, 978].

The Yachia technique is based on a completely different concept, as it utilises the Heinke-Mikowitz principle for which a longitudinal tunical incision is closed transversely to shorten the convex side of the penis. This technique, initially described by Lemberger in 1984, was popularised by Yachia in 1990, when he reported a series of 10 cases [979-984].

Pure plication techniques are simpler to perform. They are based on single or multiple plications performed without making excisions or incisions on the tunical albuginea, to limit the potential damage to the veno-

occlusive mechanism [874, 985-1001]. Another modification described the '16-dot' technique that consists of the application of two pairs of parallel Essed-Schroeder plications tensioned more or less depending on the degree of curvature [1002-1005]. Results and satisfaction rates are similar to both incision/excision techniques.

In general, using these tunical shortening techniques, complete penile straightening is achieved in > 85% of patients. Recurrence of the curvature and penile hypo-aesthesia is uncommon (~10%) and the risk of post-operative ED is low. Penile shortening is the most commonly reported adverse outcome of these procedures. Shortening of 1-1.5 cm has been reported for 22-69% of patients, which is rarely the cause of post-operative sexual dysfunction and patients may perceive the loss of length as greater than it actually is. It is therefore strongly advisable to measure and document the penile length peri-operatively, both before and after the straightening procedure, whichever technique is used (Table 17).

As mentioned above, there are multiple techniques with small modifications and all of them have been reported in retrospective studies, most of them without appropriate comparison between techniques and therefore the level of evidence is not sufficient to recommend one particular method over another.

Table 17: Results of tunical shortening procedures for PD (data from different, non-comparable studies) [874, 979-1002, 1006-1009]

	Tunical shortening procedures				
	Nesbit	**Modified Nesbit**	**Yachia**	**16-dot / mod16-dot**	**Simple plication**
No. of patients/studies	652 / 4	387 / 5	150 / 6	285 / 5	1068 / 18
Significant penile shortening (%)*†	8.7% (5-39)	3.2% (0-13)	3.5% (0-10)	5.9% (0-6)	8.9% (0-55)
Any penile shortening (%)*	21.8% (9-39)	58.% (23-74)	69% (47-97)	44.6% (40-52)	33.4% (0-90)
Penile straightening (%)*	88.5% (86-100)	97.6% (92-100)	95.5% (93-100)	96.9% (95-100)	94.7% (85-100)
Post-operative *de novo* ED (%)*	6.9% (0-17)	3% (0-13)	9.6% (0-13)	3.8% (0-13)	8.1% (0-38)
Penile hypoesthesia (%)*	11. 8% (2-60)	5.6% (0-31)	1% (0-3)	8.2% (6-13)	9% (0-47)
Overall satisfaction (%)*	83.5% (76-88)	95.4% (87-100)	86.8% (78-100)	94% (86-100)	86.4% (52-100)
Follow-up (months)*	(69-84)	(19-42)	(10-24)	(18-71)	(12-141)

**Data are expressed as weighted average. † Defined as > 30 degrees of curvature. Ranges are in parentheses. ED = Erectile dysfunction.*

8.2.3.2.2 Tunical lengthening procedures

Tunical lengthening procedures are performed on the concave side of the penis after making an incision or partial excision of the plaque, with coverage of the defect with a graft. Although tunical lengthening procedures rarely lead to long-term penile length gain, they aim to minimise penile shortening caused by plication of the tunica albuginea, and correct complex deformities. In practice, tunical lengthening procedures are often combined with penile plication or shortening procedures to correct residual curvature and therefore may also result in penile shortening [1010]. Tunical lengthening surgery is preferable in patients with significant penile shortening, severe curvature and/or complex deformities (hourglass or hinge) but without underlying ED. The definition of severe curvature has been proposed to be > 60°, although no studies have validated this threshold. On the concave side of the penis, at the point of maximum curvature, which usually coincides with the location of the plaque, an incision is made, creating a defect in the albuginea that is covered with a graft. Complete plaque removal or plaque excision may be associated with higher rates of post-operative ED due to venous leak, but partial excision in cases of florid calcification may be permissible [1011, 1012]. Patients who do not have pre-operative ED should be informed of the significant risk of post-operative ED of up to 50% [969].

A large number of different grafts have been used. The ideal graft should be resistant to traction, easy to suture and manipulate, flexible (although not too much, to avoid aneurysmal dilations), readily available, cost-effective, and morbidity should be minimal, especially when using autografts. No graft material meets all of these requirements. Moreover, the studies performed did not compare different types of grafts and biomaterials and were often single-centre retrospective studies so there is not a single graft that can be recommended for

surgeons [1013]. The use of geometric principles introduced by Egydio may help to determine the exact site of the incision, and the shape and size of the defect to be grafted [1014].

Grafts for PD surgery can be classified into four types (Table 18) [1015]:

- Autografts: taken from the individual himself, they include the dermis, vein, temporalis fascia, fascia lata, tunica vaginalis, tunica albuginea and buccal mucosa.
- Allografts: also of human origin but from a deceased donor, including the pericardium, fascia lata and dura mater.
- Xenografts: extracted from different animal species and tissues, including bovine pericardium, porcine small intestinal submucosa, bovine and porcine dermis, and TachoSil® (matrix of equine collagen).
- Synthetic grafts: these include Dacron® and Gore-Tex®.

All the autologous grafts have the inconvenience of possible graft harvesting complications. Dermal grafts are commonly associated with veno-occlusive ED (20%) due to lack of adaptability, so they have not been used in contemporary series [1013, 1016-1027]. Vein grafts have the theoretical advantage of endothelial-to-endothelial contact when grafted to underlying cavernosal tissue. The saphenous vein has been the most commonly used vein graft [1028-1043]. For some extensive albuginea defects, more than one incision may be needed. Tunica albuginea grafts have perfect histological properties but have some limitations: the size that can be harvested, the risk of weakening penile support and making future procedures (penile prosthesis implantation) more complicated [1044-1046]. Tunica vaginalis is easy to harvest and has little tendency to contract due to its low metabolic requirements, although better results can be obtained if a vascular flap is used [1047-1051]. Under the pretext that by placing the submucosal layer on the corpus cavernosum the graft feeds on it and adheres more quickly, the buccal mucosal graft has recently been used with good short-term results [1052-1058].

Cadaveric dura mater is no longer used due to concerns about the possibility of infection [1059, 1060]. Cadaveric pericardium (Tutoplast©) offers good results by coupling excellent tensile strength and multidirectional elasticity/expansion by 30% [950, 1012, 1023, 1061, 1062]. Cadaveric or autologous fascia lata or temporalis fascia offers biological stability and mechanical resistance [1063-1065].

Xenografts have become more popular in recent years. Small intestinal submucosa (SIS), a type I collagen-based xenogenic graft derived from the submucosal layer of the porcine small intestine, has been shown to promote tissue-specific regeneration and angiogenesis, and supports host cell migration, differentiation and growth of endothelial cells, resulting in tissue structurally and functionally similar to the original [1066-1075]. As mentioned above, pericardium (bovine, in this case) has good traction resistance and adaptability, and good host tolerance [1043, 1076-1079]. Grafting by collagen fleece (TachoSil©) in PD has some major advantages such as decreased operating times, easy application and an additional haemostatic effect [1080-1085].

It is generally recommended that synthetic grafts, including polyester (Dacron®) and polytetrafluoroethylene (Gore-Tex®) are avoided, due to increased risks of infection, secondary graft inflammation causing tissue fibrosis, graft contractures, and possibility of allergic reactions [982, 1086-1089].

Post-operative penile rehabilitation to improve surgical outcomes has been suggested with a number of studies describing the use of VED and PTT to prevent penile length loss of up to 1.5 cm [1090]. Daily nocturnal administration of PDE5I enhances nocturnal erections, encourages perfusion of the graft, and may minimise post-operative ED rates [1091]. Massages and stretching of the penis have also been recommended once wound healing is complete.

Table 18: Results of tunical lengthening procedures for PD (data from different, non-comparable studies) [950, 982, 1012, 1016-1085, 1092, 1093]

	Year of publication	No. of patients / studies	Success (%)*	Penile shortening (%)*	*De novo* ED (%)*	Follow-up (mo)*
Autologous grafts						
Dermis	1974-2019	718 / 12	81.2% (60-100)	59.9% (40-75)	20.5% (7-67)	(6-180)
Vein grafts	1995-2019	690 / 17	85.6% (67-100)	32.7% (0-100)	14.8% (0-37)	(12-120)
Tunica albuginea	2000-2012	56 / 3	85.2% (75-90)	16.3% (13-18)	17.8% (0-24)	(6-41)
Tunica vaginalis	1980-2016	76 / 5	86.2% (66-100)	32.2% (0-83)	9.6% (0-41)	(12-60)
Temporalis fascia / Fascia lata	1991-2004	24 / 2	100%	0%	0%	(3-10)
Buccal mucosa	2005-2016	137 / 7	94.1% (88-100)	15.2% (0-80)	5.3% (0-10)	(12-45)
Allografts (cadaveric)						
Pericardium	2001-2011	190 / 5	93.1% (56-100)	23.1% (0-33)	37.8% (30-63)	(6-58)
Fascia lata	2006	14 / 1	78.6%	28.6%	7.1%	31
Dura matter	1988-2002	57 / 2	87.5%	30%	17.4% (15-23)	(42-66)
Xenografts						
Porcine SIS	2007-2018	429 / 10	83.9% (54-91)	19.6% (0-66)	21.9% (7-54)	(9-75)
Bovine pericardium	2002-2020	318 / 6	87.4% (76.5-100)	20.1% (0-79.4)	26.5% (0-50)	(14-67)
Bovine dermis	2016	28 / 1	93%	0%	25%	32
Porcine dermis	2020	19 / 1	73.7%	78.9%	63%	85
TachoSil®	2002-2020	529 / 7	92.6% (83.3-97.5)	13.4% (0-93)	13% (0-21)	(0-63)

**Data are expressed as weighted average. Ranges are in parentheses.*
ED = Erectile dysfunction; SIS = Small intestinal submucosa.

It must be emphasised that there have been no RCTs comparing surgical outcomes in PD. The risk of ED seems to be greater for penile lengthening procedures [871]. Recurrent curvature is likely to be the result of failure to wait until the disease has stabilised before surgery is undertaken, re-activation of the condition following the development of stable disease, or the use of early re-absorbable sutures (e.g., Vicryl) that lose their tensile strength before ensuing fibrosis has resulted in acceptable strength of the repair. Accordingly, it is recommended that only non-absorbable sutures or slowly re-absorbed absorbable sutures (e.g., polydioxanone) should be used. 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-absorbable sutures (e.g., polydioxanone) [1094]. Penile numbness is a potential risk of any surgical procedure, involving mobilisation of the dorsal neurovascular bundle. This is usually a temporary neuropraxia, due to bruising of the dorsal sensory nerves. Given that the usual deformity is dorsal, the procedure most likely to induce this complication is a lengthening (grafting) procedure, or the association with (albeit rare) ventral curvature [971].

8.2.3.2.3 Penile prosthesis

Penile prosthesis (PP) implantation is typically reserved for the treatment of PD in patients with concomitant ED not responding to conventional medical therapy (PDE5I or intracavernous injections of vasoactive agents) [871]. Although inflatable prostheses (IPPs) have been considered more effective in the general population with ED, some studies support the use of malleable prostheses in these patients with similar satisfaction rates [871, 1095, 1096]. The evidence suggests that there is no real difference between the available IPPs [1097]. Surgeons can and should advise on which type of prosthesis best suits their patients but it is the patient who should ultimately choose the prosthesis to be implanted [1098].

Most patients with mild-to-moderate curvature can expect an excellent outcome simply by cylinder insertion [1041, 1099]. If the intra-operative curvature after placement of the prosthesis is < 30° no further action is indicated, since the prosthesis itself will act as an internal tissue expander to correct the curvature during the subsequent six to nine months. If, the curvature is > 30°, the first-line treatment should be modelling with the prosthesis maximally inflated (manually bent on the opposite side of the curvature for 90 seconds, often accompanied by an audible crack) [1100, 1101]. If, after performing this manoeuvre, a deviation > 30° persists,

subsequent steps to be considered include incision with or without collagen fleece coverage (if the defect is small, it can be left uncovered) or plaque incision and grafting are performed [1102-1107]. However, the defect may be covered if it is larger, and this can be accomplished using grafts commonly used in grafting surgery (described above) which prevent herniation and recurrent deformity and buckling due to the scarring of the defect [1108, 1109]. The risk of complications (infection, malformation, etc.) is not increased compared to that in the general population. However, a small risk of urethral perforation (3%) has been reported in patients with 'modelling' over the inflated prosthesis [1100].

In selected cases of end-stage PD with ED and significant penile shortening, a lengthening procedure, which involves simultaneous PP implantation and penile length restoration, such as the "sliding" technique has been proposed [1110]. However, the "sliding" technique is not recommended due to reported cases of glans necrosis because of the concomitant release of the neurovascular bundle and urethra, new approaches for these patients have been recently described, such as the MoST (Modified Sliding Technique), MUST (Multiple-Slit Technique) or MIT (Multiple-Incision Technique) techniques, but these should only be used by experienced high-volume surgeons and after full patient counselling [1111-1114].

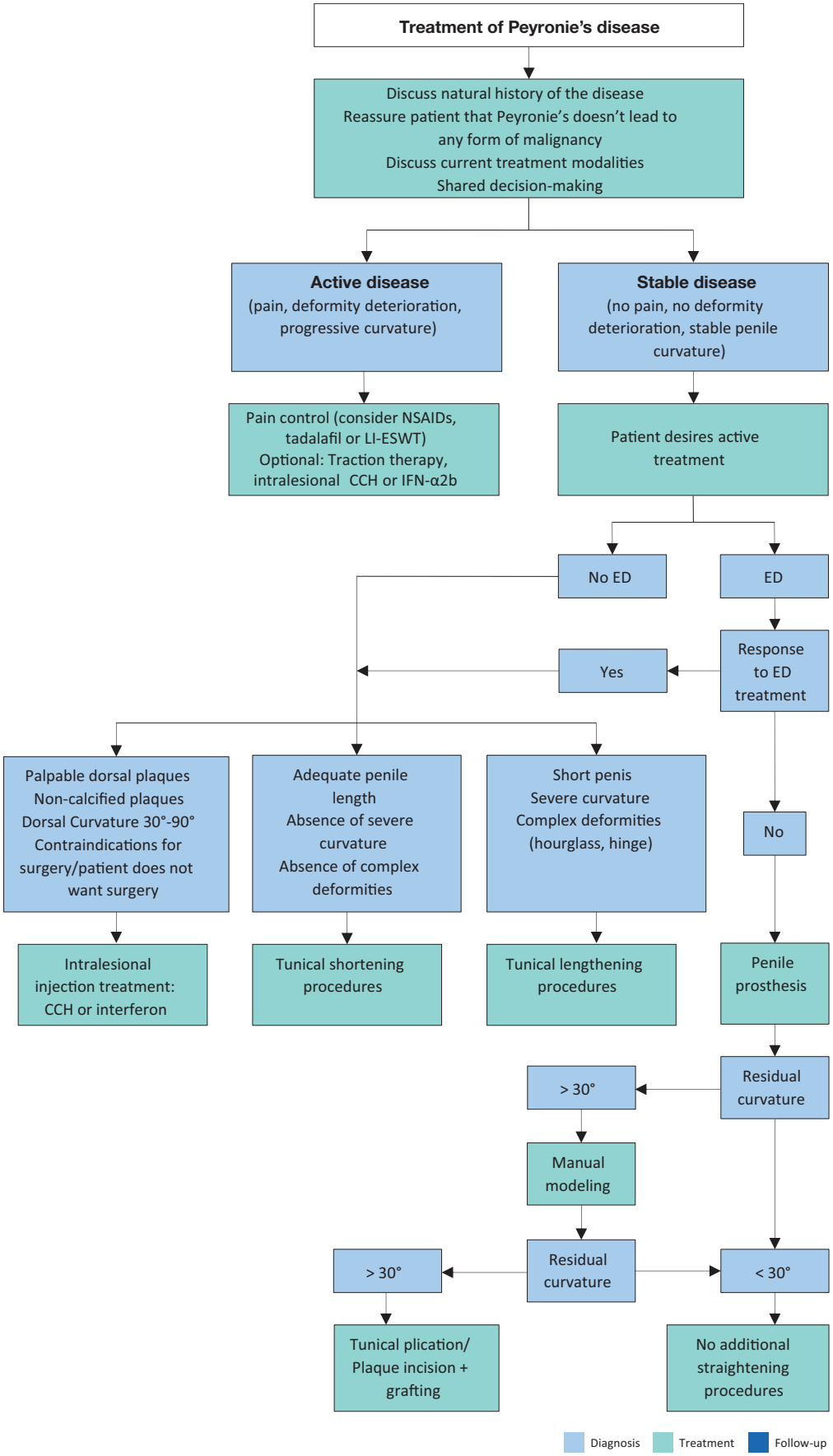
While patient satisfaction after IPP placement in the general population is high, satisfaction rates have been found to be significantly lower in those with PD. Despite this, depression rates decreased after surgery in PD patients (from 19.3%-10.9%) [1115]. The main cause of dissatisfaction after PPI in the general population is shortening; therefore, patients with PD undergoing PP surgery must be counselled that the prostheses are not designed to restore the previous penile length [1115, 1116].

8.2.3.2.4 Summary of evidence and recommendations for surgical treatment of Peyronie's disease

Summary of evidence	**LE**
Surgery for PD should only be offered in patients with stable disease and with functional impairment.	2b
In patients with concomitant PD and ED without response to medical treatment, penile prosthesis implantation with or without additional straightening manoeuvres is the technique of choice.	2a
In other cases, factors such as penile length, rigidity of erection, degree of curvature, presence of complex deformities and patient choice must be taken into account when deciding whether to undertake tunical shortening or lengthening procedures.	3

Recommendation	**Strength rating**
Perform surgery only when Peyronie's disease (PD) has been stable for at least three months (without pain or deformity deterioration), which is usually the case after twelve months from the onset of symptoms, and intercourse is compromised due to the deformity.	Strong
Assess penile length, curvature severity, erectile function (including response to pharmacotherapy in case of erectile dysfunction [ED]) and patient expectations prior to surgery.	Strong
Use tunical shortening procedures as the first treatment option for congenital penile curvature and for PD with adequate penile length and rigidity, less severe curvatures and absence of complex deformities (hourglass or hinge). The type of procedure used is dependent on surgeon and patient preference, as no procedure has proven superior to its counterparts.	Weak
Use tunical lengthening procedures for patients with PD and normal erectile function, without adequate penile length, severe curvature or presence of complex deformities (hourglass or hinge). The type of graft used is dependent on the surgeon and patient preference, as no graft has proven superior to its counterparts.	Weak
Do not use the sliding technique as there is a significant risk of life changing complications (e.g., glans necrosis).	Strong
Do not use synthetic grafts in PD reconstructive surgery.	Strong
Use penile prosthesis implantation, with or without any additional straightening procedures (modelling, plication, incision or excision with or without grafting), in PD patients with ED not responding to pharmacotherapy.	Strong

Figure 10: Treatment algorithm for Peyronie's disease



ED = erectile dysfunction; LI-ESWT= low-intensity extracorporeal shockwave treatment; NSAIDs =non-steroidal anti-inflammatory drugs; CCH = Collagenase Clostridium histolyticum; IFN-α2b = Interferon-α2b.

9. PENILE SIZE ABNORMALITIES AND DYSMORPHOPHOBIA

9.1 Definition, epidemiology and classification

9.1.1 ***History***

Throughout history, the size of the penis has symbolised a marker of masculinity [1117] and has created intense debate in societies with different social and cultural implications [1118]. Indeed, along with the capacity for vaginal penetration, the penis is linked to an ancestral sense of men's fertility and sexual performance, making the size of the penis a source of distinguishing male identity [1119, 1120]. Evidence of male supremacy and dominance as represented by phallometric designs can be found across cultures and history and is still currently supported by contemporary media, including the pornographic industry [1121, 1122].

Overall, cosmetic surgery has the potential to restore self-esteem, reduce anxiety, social phobia and depressive mood states regarding body concerns, increasing individuals' well-being and quality of life (QoL) [1123, 1124]. Yet, some candidates for cosmetic surgery may have psychopathological conditions and surgery may result in negative outcomes [1124, 1125].

In the real-life setting, it is interesting to note that 84% of women report being satisfied with their male partners' penile size whereas 55% of the male partners were satisfied with their penile size and 45% of them report that they would like to have a larger penis [1126]. In this context, men with a high level of social-desirability were more likely than others to self-report having a larger penis [1127]. A recent study also demonstrated that reducing the depth of penetration led to a statistically significant 18% reduction of overall sexual pleasure with an average 15% reduction in the length of the penis [1128].

Additionally, the subjective impression of penile size may have a negative effect on sexual functioning and QoL, impacting sexual life in about 10% of men [1129-1131]. This prevalence sharply rises in patients seeking penile augmentation procedures [1132, 1133].

Furthermore, the fact that a subgroup of men does not achieve reasonable levels of satisfaction and emotional adjustment after penile augmentation procedures, underlines that with certain psychopathological conditions men will not benefit from such invasive procedures [1134]. These men may represent a psychologically vulnerable group of individuals in whom penile augmentation procedures will have negative effects and, as such, require clinical and psychological support. Clinicians should possess the skills to anticipate and address such vulnerability through a personalized psychological assessment. Additionally, they should take into account cultural norms to facilitate an understanding of patient expectations [1135].

With the increased use of penile augmentation procedures worldwide, either medical or surgical, it becomes crucial to create evidence-based recommendations to guide clinicians in this challenging and controversial area.

9.1.2 ***Definition***

To date short penis condition represents both a diagnostic and treatment challenge [1136, 1137]. An accurate measurement of the penile shaft is a mandatory step in the assessment of patients complaining of a short penis and defining the norm [1138]. Indeed, a standard tool to address penile measurements and to counsel patients seeking penile augmentation procedures is needed. To date, the standard penile size has yet to be clearly defined. Even though several investigators have attempted to provide objective measurements to define a normal penile size, there is still no consensus on this (Table 19).

Table 19: Summary of papers reporting objective penile measurements

Authors	Year	Patients, n	Age, years	Flaccid length, cm	Stretched length, cm	Erect length, cm	Flaccid circum-ference, cm	Erect circum-ference, cm
Loeb [1139]	1899	50; Caucasian	(17 – 35)	9.41	NA	NA	NA	NA
Ajmani *et al.* [1140]	1985	320; African - Nigeria	(17-23)	8.19 ±0.94	NA	NA	8.83 ±0.02	NA
Schonfeld *et al.* [1141]	1942	54; Caucasian - USA	(20 – 25)	NA	13.02	NA	NA	NA
Kinsey *et al.* [209]	1948	2770; Caucasian	(20 – 59)	9.7	16.74	NA	NA	NA
Bondil *et al.* [1142]	1992	905; Caucasian - France	53.18 ±18.19	10.74 ±1.84	16.74 ±2.29	NA	NA	NA
Richters *et al.* [1143]	1995	156; Caucasian - Australia	NA	NA	NA	15.99	NA	NA
Wessels *et al.* [1144]	1996	80; Caucasian - USA	54 ±14.37	8.85 ±2.38	12.45 ±2.71	12.89 ±2.91	9.71 ±1.71	12.30 ±1.31
Smith *et al.* [1145]	1998	184; Caucasian - Australia	NA	NA	NA	15.71 ±2.31	NA	NA
Bogaert *et al.* [1146]	1999	3417; Caucasian - USA	30.45 ±11.27	9.83 ±1.80	NA	15.60 ±1.88	NA	NA
Ponchietti *et al.* [1147]	2001	3300; Caucasian - Italy	(17 - 19)	9 (5-12)	12.5 (8 - 16.5)	NA	10 ±0.75	NA
Schneider *et al.* [1148]	2001	111; Caucasian - Germany	18.24 ±0.43	8.60 ±1.50	NA	14.48 ±1.99	NA	NA
Spyropoulos *et al.* [1149]	2002	52; Caucasian - Greece	25.9 ±4.4	7.76 ±1.3	12.18 ±1.7	NA	8.68 ±1.12	NA
Awwad *et al.* [1150]	2005	271; Arab - Jordan	44.6 ±16.3	9.3 ±1.9	13.5 ±2.3	NA	8.9 ±1.5	NA
Mehraban *et al.* [1151]	2007	1500; Arab - Iran	29.61 ±5.50	NA	11.58 ±1.45	NA	8.66 ±1.01	NA
Promodu *et al.* [1152]	2007	301; Indian	31.58 ±6.38	8.21 ±1.44	10.88 ±1.42	12.93 ±1.63	9.14 ±1.02	11.49 ±1.04
Aslan *et al.* [1153]	2011	1132; Arab - Turkish	20.3 ±0.9	9.3 ±1.3	13.7 ±1.6	NA	NA	NA
Choi *et al.* [1154]	2011	144; oriental - Korea	57.3 ±16.5	7.7 ±1.7	11.7 ±1.9	NA	NA	NA
Shalaby *et al.* [1155]	2014	2000; African - Egypt	31.6 ± 4.2	NA	13.84 ±1.35	NA	NA	NA
Veale *et al.* [1136]	2014	15521; Caucasian - UK	NA	9.16 ±1.57	13.24 ±1.89	13.12 ±1.66	9.31 ±0.90	11.66 ±1.10
Habous *et al.* [1156]	2015	778; Arab - Saudi Arabia	43.7 (20–82)	NA	NA	14.34 ±1.86	NA	11.50 ±1.74
Hussein *et al.* [1157]	2017	223; Arab - Iraq	41.3 ±15	9.8 ±2.0	12.6 ±1.9	NA	NA	NA
Alves Barboza *et al.* [1158]	2018	Tot 627 - Brazil African 167; Caucasian 283	53.6 ±15 53.8 ±13.8 53.7 ±15.5	NA NA NA	NA 16.5 ±1.7 15.8 ±1.6	NA NA NA	NA NA NA	NA NA NA
Di Mauro *et al.* [1159]	2021	4685; Caucasian - Italy	19 ±6.2	9.47 ±2.69	16.78 ±2.55	NA	9.59 ±3.08	12.03 ±3.82

Nguyen Hoai *et al.* [1160]	2021	14597; Asian - Vietnam	33.1 ±10.7	9.03 (5.10-13.20)	14.67 (8.30-19.90)	NA	8.39 (5.34-11.3)	NA
Takure [1161]	2021	271; African - Nigeria	57.3 ±16.4	10.3 ±2.4	13.7 ±2.5	NA	NA	NA
Sole *et al.* [1162]	2022	800; Caucasian - Argentina	54.2 ±17.6	11.4 ±2	15.2 ±2.2	NA	10.1 ±1.3	NA

Measurements are expressed as median/mean, (IQR)/±SD

The other factor that strongly affects penile measurements is the interobserver variability and the underestimation of the stretched penile length (SPL) when compared to the erect state [1163].

Despite the aforementioned limitations, SPL, defined as the distance between the pubic symphysis and the apex of the glans, represents the most overlapping measurement of the erect penis. Accordingly, a SPL of less than 2.5 standard deviations (SD) below the mean for the male's age and race is considered as micropenis [1164, 1165].

Summary of evidence	**LE**
There is a difference between true micropenis (anatomical-endocrinological)/short penis (complaint)/ buried penis (complaint short penis + obesity) (panel consensus). Small penis anxiety/syndrome refers to a man's excessive anxiety regarding his normal-sized penis.	4
A true micropenis is a congenital condition where the stretched penile length is 2.5 SD cm less than the average length in the population group and is the result of an underlying genetic or endocrine condition.	3
A buried penis is a normal-sized penis where there is a functional and visible loss of penile length due to an underlying pathological condition such as obesity or traumatic loss of length. The penis is covered by prepubic, scrotal or penile subcutaneous tissue or skin.	3
Penile Dysmorphic Disorder is a shorthand concept applied to Body Dysmorphic Disorder cases characterised by a strong focus on a perceived deficiency or flaw in a normal size or shape penis, resulting in mental health impairment and significant damage in important areas of the individual's life.	3

9.1.3 Epidemiology and Classification

The overall incidence of micropenis in the male population is not clearly documented. Epidemiological studies demonstrate that between 0.015% - 0.66% of male newborns have a micropenis [1166, 1167]. There are concerns that the prevalence of this congenital abnormality is increasing due to *in-utero* exposure to endocrine-disrupting chemicals before and during pregnancy [1167]. Despite the limited prevalence of micropenis, there is a major demand for penile augmentation procedures worldwide. This phenomenon can be partially explained by the increased interest in pornography in recent years and the altered perception of a normal penile size [1118, 1168, 1169].

Due to the heterogeneity of clinical situations related to short penis conditions, a classification based on the underlying aetiology is provided below (Table 20).

Table 20: Classification of the clinical conditions underlying a short penis condition or dysmorphophobia in the adult

Group name	**Aetiology**	**Definition**	**Pathogenesis**	**Prevalence, %**
False penile shortness	Acquired	Reduced exposure of the penile shaft in the presence of normal penile size	Adult acquired buried penis	NA
Intrinsic penile shortness	Congenital	Small penis due to an incomplete genital development secondary to a congenital condition	• Hypogonadotropic hypogonadism • Genetic syndromes • Bladder exstrophy–epispadias complex	0.9 - 2.1

Intrinsic penile shortness	Acquired	Shortening/shrinking of the corpora cavernosa due to an acquired pathological process	• Peyronie's Disease • Radical prostatectomy • Radical cystectomy • Radiation therapy • Low flow priapism • Multiple penile operations (e.g., urethral surgery or PP infection) • Penile traumatic event (traumatic or surgical amputation for penile cancer)	NA
Body dysmorphic disorder	Acquired	Perceived defect or flaw in the individual's physical appearance followed by significant distress or impairment in important areas of the individual's life	• Penile Dysmorphic Disorder	1.8 – 9.5

9.1.3.1 False penile shortness - congenital or acquired

Among causes underlying a false penile shortness, the buried penis is the only well-known condition. Historically, a buried penis has been considered a congenital disease affecting children: the so-called "concealed penis" or "webbed penis" [1170, 1171]. Indeed, an abnormal development of the dartos fascia may lead to the entrapment of the penile shaft to the peri-genital tissue leading to this clinical manifestation. On the other hand, a buried penis in the adult is widely recognised as an acquired condition, termed the adult acquired buried penis (AABP) [1172].

The aetiology underlying the development of AABP is deemed to be related to a chronic inflammatory state of the penile dartos which leads to a progressive retraction and scarring of the peri-genital teguments [1173, 1174]. The progressive entrapment of the phallus causes a moist environment which facilitates bacterial and fungal growth causing chronic inflammation [1175]. The ensuing fibrosis results in further entrapment of the penile shaft in the peri-genital tissue [1174, 1175].

Although the exact prevalence of AABP is unknown, its incidence seems to be increasing along with the growing prevalence of obesity, which represents the main risk factor [1176]. Other factors contributing to AABP include aggressive circumcision, following surgical treatment in the obese or penile cancer (PC), or chronic dermatological conditions such as lichen sclerosis (LS) [1177-1179].

The AABP is commonly associated with erectile and voiding dysfunctions, difficulties in maintaining adequate genital hygiene and a poor QoL [1177-1179]. A summary of risk factors for AABP and underlying issues requiring surgery is detailed in Table 21.

Table 21: Summary of studies reporting clinical characteristics of patients with AABP

Study	Year	n	Age, yr	BMI	DM (%)	HT (%)	Smoking habits (%)	History of penile cancer (%)	History of LS (%)	Underlying issues requiring surgery (%)
Ngaage *et al.* [1180]	2021	15	53 ±15.7	37.4 ±4.3	7 (54%)	NR	0	6 (46%)	NR	Urinary or sexual difficulties 9 (60.0%)

Kara *et al.* [1181]	2021	13	22.4 ±4.8	26 ±6.2	7%	7%	NR	0	NR	Cosmetic issues 13 (100%), self-esteem/ psychological well-being 13 (100%), urinary or sexual difficulties 13 (100%)
Zhang *et al.* [1182]	2020	26	33 ±5.7	29 ±5.4	NR	NR	NR	NA	NR	-
Monn *et al.* [1183]	2020	67	54.76 ±12.7	40.4 ±6.7	20 (47.6%)	NR	NR	NA	NR	Urinary difficulties 50 (74.6%), pain 21(31.3%), sexual difficulties 52 (77.6%)
Gao *et al.* [1184]	2020	32	32.5 (26-38)	-	NR	NR	NR	NR	NR	Cosmetic issues 32 (100%)
Erpelding *et al.* [1185]	2019	16	54 (44-62)	47.7 (25.5-53.3)	9 (56%)	NR	4 (25%)	NR	2 (12.5%)	-
Hesse *et al.* [1186]	2019	27	56 ±15	49 ±14	12 (44%)	16 (59%)	NR	NR	NR	Pain 12 (44%), sexual difficulties 8 (30%), difficulty in ambulating 9 (33%)
Zhang *et al.* [1187]	2019	15	33.2 ±4.6	28.9 ±5.3	NR	NR	NR	0	NR	-
Monn *et al.* [1188]	2019	13	43.4 ±15.3	42.0 ±7.3	6 (46.2%)	NR	4 (30.8%)	NR	NR	-
Aube *et al.* [1189]	2019	24	61.5 (54–67)	38.1 (33.6–43.7)	NR	NR	13 (54.2%)	NR	17 (70.8%)	Personal hygiene 19 (79.2%), urinary difficulties 14 (58.3%), sexual difficulties 19 (79.2%)
Cocci *et al.* [1190]	2019	47	51.8 ±18.4	30 ±2.3	16 (34%)	18 (38.29%)	NR	NR	10 (10.63%)	Sexual difficulties 13 (27.66%), urinary difficulties 13 (27.66%), combination of urinary and sexual difficulties 12 (25.54%)
Pariser *et al.* [1191]	2018	64	53 (42-63)	45 (38-53)	32 (50%)	NR	16 (25%)	0	NR	-

Theisen *et al.* [1192]	2018	16	48.5	44.7	9 (56%)	9 (56%)	NR	NR	12 (78%)	-
Fuller *et al.* [1193]	2017	12	-	45.4 ±13.8	NR	NR	NR	NR	NR	-
Voznesensky *et al.* [1194]	2017	14	50 ±10.5	55 ±13.7	NR	NR	NR	NR	NR	-
Hampson *et al.* [1177]	2017	42	-	-	48%	67%	NR	1	33%	Personal hygiene (67%); urinary or sexual difficulties (52%)
Ghanem *et al.* [1195]	2017	10	29.4 ±6.1	26.5 ±3.7	NR	NR	NR	NR	NR	-
Tausch *et al.* [1172]	2016	56	-	39 (22-63)	NR	NR	NR	NR	NR	-
Westerman *et al.* [1196]	2015	15	51 (26-75)	42.6 (29.8-53.9)	8 (53.3%)	NR	NR	0	13 (87%)	Cosmetic issues 11 (100%), urinary difficulties 6 (40%), sexual difficulties 3 (20%)
Rybak *et al.* [1197]	2014	11	54.2 ±44.7	49.2 (42.4-64.5)	NR	NR	NR	0	0	-
Shaeer *et al.* [1198]	2009	64	(22-54)	-	NR	NR	NR	0	0	Cosmetic issues 64 (100%)

Measurements are expressed as median/mean, (IQR)/±SD
BMI = body mass index; DM = diabetes mellitus; HT = hypertension; LS = lichen sclerosis.

The aim of AABP treatment is to restore the functional genital anatomy and to improve QoL [1177, 1178]. So far, different authors have proposed a number of classifications for AABP based upon both clinical presentation and the surgical procedure required [1172, 1191].

9.1.3.2 Intrinsic penile shortness – congenital

This category encompasses the so-called "true micropenis" [1199-1201]. Despite male genital malformations being recognised as the most common birth defects, they represent a rare clinical entity with a prevalence between 0.9% and 2.1% [1202, 1203]. Normal genital development is under the influence of hormonal stimulation during the fetal and pubertal periods [1204]. Several genetic syndromes may cause disturbance of the physiological hormonal axis needed for a normal genital development [1199, 1205]. Micropenis may also exist as an isolated finding without a definitive etiological cause in up to 25% of the cases. The classification of the clinical conditions associated with intrinsic penile shortness in the adult is presented in Table 22.

Table 22: Classification of the clinical conditions underlying intrinsic penile shortness in the adult

Aetiology	Disturbs
Hypogonadotropic hypogonadism	• Genetic diseases • Iatrogenic or traumatic injury to pituitary gland or hypothalamus
Hypergonadotropic Hypogonadism	• Chromosomal alterations (e.g., Klinefelter Syndrome) • Androgen Synthesis Defects • Dysgenetic gonads
Syndromic or Multiple Congenital Anomalies	• Bladder exstrophy–epispadias complex • Hypospadias
Unknown	-

Amongst the pre-existing clinical entities associated with micropenis, the bladder exstrophy–epispadias complex (BEEC) is the most studied [1177, 1178, 1201]. It represents a spectrum of genitourinary malformations ranging in severity from epispadias to bladder exstrophy or exstrophy of the cloaca. It is considered as a rare disease, with a prevalence at birth of 1/10,000 [1199, 1201, 1203, 1206]. Even though surgical reconstruction aims to improve body image, this clinical entity is frequently burdened by psychosocial and psychosexual dysfunctions in the long term [1207-1213]. Additionally, male infertility is frequently associated due to poor sperm quantity or quality and hormonal impairment [1214].

9.1.3.3 Intrinsic penile shortness – acquired

This category includes a series of pathological entities that lead to the shortening of the corpora cavernosa. The mechanism underlying intrinsic penile shortening can be acute, as in the case of penile trauma or surgical amputation due to penile cancer or chronic due to a progressive fibrotic process involving the corpora cavernosa [1215-1217].

Traumatic genital injuries may commonly result from traffic accidents and gunshot wounds [1217]. Rarely, a penile amputation can be the result of circumcision and genital surgical procedures such as hypospadias repair, penile prosthesis implantation or urethroplasty, and may result in a decrease in penile length [1218-1222].

Among chronic causes of penile shortening, Peyronie's disease (PD), treatments for prostate cancer, particularly radical prostatectomy (RP) and radical cystectomy represent the most common [1132, 1215, 1216, 1223-1231].

9.1.3.4 Body dysmorphic disorder

Body dysmorphic disorder (BDD) is a clinical diagnosis defined by the American Psychiatric Association (APA; DSM-5) as the strong distress generated by perceived defect(s) or flaw(s) in the individual's physical appearance. This flaw is not observable to others, or, in case it exists, it appears only slightly [1232]. This condition is followed by significant impairment in important areas of the individual's social or occupational life. Body dysmorphic disorder has been allocated to the Obsessive Compulsive and Related Disorders section [1232]. Muscle dysmorphia is a typology within BDD characterising individuals – usually men – with a strong pre-occupation with their perceived small muscles and body shape. Sometimes, men with BDD/muscle dysmorphia also present with an exaggerated focus on the size or shape of their penis. In those cases, Penile Dysmorphic Disorder (PDD) can be used as a shorthand concept – not listed in APA's DSM-5 coding system. Both BDD and PDD are conceptually different from small penis anxiety (SPA) or small penis syndrome, which refers to a man's excessive anxiety regarding his normal-sized penis. Small penis anxiety is not included under APA's nomenclature but men with SPA may be at risk for BDD [1233]. All these definitions exclude men with true micropenis [1232, 1234, 1235]. Prevalence data shows that 2.2% of men in the USA and 1.8% in Germany suffer from BDD [1232]. Between 3%-16% of patients undergoing cosmetic surgery are expected to present BDD, a higher rate in men (15.3%) than in women (10.9%) [1236].

These psychopathological entities must be differentiated from Gender Dysphoria, i.e., the clinical distress associated with the incongruence between gender identity and the gender assigned at birth; and from Koro, i.e., sudden anxiety about the penis falling back into the abdomen [1232].

*9.1.4 **Summary of evidence and recommendations for classification***

Summary of evidence	**LE**
Male genital malformations represent a rare clinical entity with an overall prevalence between 0.9% and 2.1%.	3
Obesity, lichen sclerosis and penile cancer treatment are risk factors for AABP.	4
Adult acquired buried penis (AABP) is commonly associated with erectile and voiding dysfunctions, difficulties in maintaining adequate genital hygiene and a poor quality of life.	3
Adult acquired buried penis condition can be staged upon both clinical presentation and the surgical procedure required according to available classification systems	3
Bladder exstrophy–epispadias complex (BEEC) is a rare clinical condition frequently associated with male genital malformations, particularly micropenis.	2b
Penile trauma and surgical amputation due to penile cancer are the most common acute causes of intrinsic penile shortening.	3
The most frequent aetiologies leading to a chronic intrinsic penile shortening are PD, treatments for prostate cancer (RP, radiation therapy and androgen-deprivation therapy) and radical cystectomy.	2b

Body dysmorphic disorder (BDD) is a clinical entity associated with a significant distress or impairment in important areas of the individual's life.	2b
Penile Dysmorphic Disorder (PDD) can be used as a shorthand concept to describe BDD patients mainly focused on penile size/shape.	4
Body dysmorphic disorder /PDD can be revealed in patients requiring cosmetic surgery.	3

Recommendations	Strength rating
A detailed genital examination should be considered in all men and particularly in men with BMI > 30, lichen sclerosis or penile cancer history and complaints of urinary/sexual difficulties or poor cosmesis to exclude the presence of an adult acquired buried penis (AABP) condition.	Strong
Use classification systems to classify AABP clinical presentation and surgical management.	Weak
Inquire on the presence of body dysmorphic disorder/penile dysmorphic disorder in patients with normal-sized penis complaining of short penile size.	Strong

9.2 Diagnosis

*9.2.1 **Medical history, physical examination and psychological assessment***

9.2.1.1 Medical History

The first step in the evaluation of short penis is a detailed medical history [1237]. Common causes of penile shortness should be screened and observed (e.g., history of phimosis, priapism, hypospadias/epispadias, penile trauma, penile cancer, prostate cancer, penile pain with or without acquired penile curvature suggestive of PD). A past or present diagnosis of BDD should also be noted.

9.2.1.2 Sexual history

Besides a comprehensive clinical interview with open questions regarding sexual education, development, or previous sexual experiences and fantasies, psychometric tools can be used. These include measurements of sexual functioning (e.g., The International Index of Erectile Function [IIEF]), sexual distress (e.g., The Sexual Distress Scale for men), and sexual satisfaction (e.g., Global Measure of Sexual Satisfaction) [307, 1238, 1239]. The propensities for sexual excitation and sexual inhibition may be further considered, (e.g., Sexual Inhibition/ Sexual Excitation Scales), as well as measurements of relationship satisfaction (e.g., Global Measure of Relationship Satisfaction) [1239, 1240]. Special focus should be put on the assessment of sexual performance expectations (e.g., The Dysfunctional Sexual Beliefs Questionnaire) [1241]. As a complementary assessment, body image perception can be further considered (e.g., The Body-Image Questionnaire).

9.2.1.3 Physical examination and penile size measurements

An accurate physical examination focused on the genital area is essential to the patient's initial assessment. The assessment of penile size and shape is mandatory to plan any subsequent medical or surgical treatment but methods for penile measurements seem to vary amongst surgeons [1138, 1242]. The EAU Guidelines Panel on Sexual and Reproductive Health considers a stretch penile length measurement as the bare minimum. If possible, the Panel also advocates additional measurements in both flaccid and erect state after intracavernosal injection of erectogenic agents, compulsory before any surgical indication. Stretched penile length (SPL) can be measured both dorsally and/or ventrally from the penopubic skin junction-to-glans tip (STT) or dorsally from the pubic bone-to-glans tip (BTT) using either a measuring tape or a Vernier calliper. Overall, the measurement of penile size has not been standardised and to date there is no consensus definition due to high heterogeneity in terms of data assessment and reporting methodologies amongst different studies [1242].

Moreover, penile girth should be noted in every patient. As for girth, both distal (coronal) and mid-shaft measurements should be recorded. Furthermore, both measures of circumference can be compared to the head-to-base ratio. The former can help classify penile shape which can be documented through photography [1243]. Although used as a surrogate, STT underestimates erect penile length by about 20% [876, 1244]. Nonetheless, it is important to note that BTT seems to have a better correlation with erect penile length, especially in overweight and obese men [876].

Table 23: Penile size measurement

Length
State Erect, stretched or flaccid ***Anatomic Landmarks*** Dorsally and/or ventrally from the penopubic skin junction-to-glans tip (STT) Dorsally from the pubic bone-to-glans tip (BTT)
Girth
State Erect or flaccid ***Anatomic Landmarks*** Proximal (penopubic skin junction) Middle shaft Distal (Coronal or subcoronal)
Shape
Head-to-base ratio Standardised photography

9.2.1.4 Psychological assessment

A sub-group of men requesting penile augmentation procedures, usually surgery, present with strong psychological vulnerability, including BDD [1233]. This subgroup of men may be at risk for increasing psychopathology and suicide attempts and will be unlikely to achieve their surgery expectations [1245]. Currently, there is a set of freely available self-reported tools that may be used to screen patients at risk for psychopathology or poor surgical outcomes, including the Body Dysmorphic Disorder Questionnaire and The Cosmetic Procedure Screening Scale for Penile Dysmorphic Disorder, screening for psychopathological cases regarding body and penile dysmorphic disorder [1233, 1246]. Likewise, The Male Genital Self-Image Scale, and the Index of Male Genital Image, measure men's perceptions and satisfaction regarding their genitals [1247, 1248]. In addition, the Beliefs About Penile Size Scale captures beliefs about the size of the penis as well as internal psychological processes [1249]. However, evidence on BDD/PDD, further psychopathological comorbidities, and the differential diagnosis regarding personality disorders, and disorders from the obsessive-compulsive, psychotic, or emotional spectrum, should be performed by an accredited mental health expert. In addition, the subjective penile size perception should be evaluated [1134].

9.2.1.5 Counselling and outcomes assessment - Validated questionnaires

The Augmentation Phalloplasty Patient Selection and Satisfaction Inventory (APPSSI) questionnaire is a 5-item questionnaire proposed for the assessment and counselling about penile augmentation surgical treatment [1250]. The Beliefs about Penis Size (BAPS) is a 10-item questionnaire created for audit and outcome research to assess men's beliefs about penile size [1249]. Both questionnaires have failed to correlate with penile size and lack of objective validation has restricted their use.

Other well-known self-reported psychosexual questionnaires may be considered: the IIEF-15 and the Male Sexual Health Questionnaire (MSHQ) should be administered to record baseline sexual function status and can also be used to assess its changes after treatment; the Erectile Dysfunction Inventory of Treatment Satisfaction (EDITS) can also be helpful to assess patient and partner's treatment satisfaction [307, 1251, 1252].

9.2.2 ***Imaging***

There is a lack of evidence regarding the use of imaging techniques in the assessment of patients complaining about penile shortness. Although a penile Doppler ultrasound or a penile magnetic resonance imaging may provide additional data regarding the penile anatomy and the extent of penile burying, there is no evidence that this additional information could contribute to the physical examination to justify its routine use in this clinical scenario [1138, 1253-1256].

Summary of evidence	LE
Medical/sexual history taking and physical examination are essential parts of the evaluation of men with a short penis complaint.	4
Among stretched penile measurements dorsal and/or ventrally from the penopubic skin junction-to-glans tip (STT) may underestimate erect penile length.	2b
Among stretched penile measurements dorsally from the pubic bone-to-glans tip (BTT) has a better correlation with erect penile length, especially in overweight and obese men.	2b
Flaccid and erect state measurements to assess penile length may add useful information on penile size.	4
Penile girth assessment may add useful information on penile size and shape.	4
The Body Dysmorphic Disorder Questionnaire, The Cosmetic Procedure Screening Scale for Penile Dysmorphic Disorder, The Male Genital Self-Image Scale and the Index of Male Genital Image are self-reported tools useful to screen patients at risk for psychopathology.	2b
Mental health counselling helps detect men requesting penile augmentation procedures present with strong psychological vulnerability, including BDD/PDD.	2b
Validated questionnaire (e.g., APPSSI, BAPS, IIEF-15, MSHQ, EDITS) help assess baseline sexual function and beliefs about penile size.	4

Recommendations	Strength rating
Take a comprehensive medical and sexual history from every patient presenting complaining of short penile size.	Strong
Use stretched penile measurements (skin junction-to-glans tip or dorsally from the pubic bone-to-glans tip) to define penile length.	Weak
Measure flaccid and erect measurements to assess penile length in detail.	Weak
Measure penile girth in every patient presenting complaining of a short penile size.	Weak
Use validated questionnaires to screen for body dysmorphic disorder (BDD) in cases of a normal-sized penis.	Weak
Use validated questionnaires (e.g., IIEF-15, BAPS) to assess baseline sexual function and beliefs concerning penile size.	Weak
Refer patients with suspected BDD for mental health counselling.	Strong

9.3 Management

*9.3.1 **Non-surgical Treatments***

9.3.1.1 Psychotherapy

Penile augmentation is often motivated by the desire to improve self-perception and self-esteem [1257]. Cosmetic treatments may help increase individuals' well-being and QoL, improving self-esteem and emotional states [1123, 1124, 1138]. Still, psychotherapy is recommended when psychopathological comorbidities are detected, or when aversive relationship dynamics may underly the request for penile augmentation. Addressing patients' and partners' motivations and expectations regarding penile augmentation seems to be a key psychotherapeutic target while no other empirical evidence is described. Similarly, men with BDD and SPA present a significant discrepancy between the perceived and ideal size of the penis, internalising the belief they should have a larger penis [1258]. Cognitive behaviour therapy for BDD could be applied to cases of anxiety regarding penis size, although no clinical trials have been reported [1259]. In all, it is worth noting that psychotherapy should normalise the great variability of genital shape and size [1133]. Managing patient expectations could be a means to improve results and well-being associated with the surgery process.

9.3.1.2 Penile traction therapy

Despite the various surgical techniques, there are also non-invasive methods that are used to enhance penile length, including penile traction therapy (PTT) [1260]. In a pilot phase-II prospective study that evaluated the efficacy and tolerability of a penile-extender device in the treatment of short penis, Gontero *et al.*, used the same traction device for at least 4 hours/day for 6 months and achieved a significant gain in length, of +2.3 and +1.7 cm for the flaccid and stretched penis, respectively (both $p < 0.001$) [1261]. However, the change in the penile girth was not significant. In a further prospective study, these results were confirmed by Nikoobakht *et al.*, who found a significant improvement in the mean length both for the flaccid (8.8 ± 1.2 cm to 10.5 ± 1.2 cm, $P < 0.05$) and the stretched state (11.5 ± 1.0 cm to 13.2 ± 1.4 cm, $p < 0.05$) following 3 months of use of a penile traction device [1262]. At six-month follow-up, compared to baseline, a mean gain of +1.7 ± 0.8, +1.3 ± 0.4, and +1.2 ± 0.4

cm was reported for the flaccid, stretched, and erect penile lengths, respectively ($p < 0.001$, for all). The broad spectrum of available PTT studies is summarised in Table 24.

Overall, PTT seems effective in lengthening the penis both in the flaccid and stretched state with minimal side effects. Yet it is not effective for penile girth enhancement. However, the quality of evidence is poor due to the lack of RCTs, and the availability of only heterogeneous and small PTT cohorts has also been proven effective in the restoration of length or correction of deformities due to several diseases, including PD, or post-RP conditions [955, 1263-1265].

Table 24: Penile traction therapy (PPT)

Author (year)	Year	n	Study design	Device	Treatment protocol	Mean age ± SD	Mean gain in penile dimensions cm (SD)
Nowroozi *et al.* [1266]	2015	54	Prospective	AndroPenis	4-6 hours per day for 6 months	30.1 ± 4.8	Flaccid length: 1.7 ± 0.8 Stretched length: 1.3 ± 0.4 Erected length: 1.2 ± 0.4
Nikoobakht *et al.* [1262]	2011	23	Prospective	Golden Erect	4–6 hours per day during the first 2 weeks and then 9 hours per day until the end of the third month	26.5 ± 8.1	Flaccid length: 1.7 Stretched length: 1.71 Circumference: -0.22 Glans penis circumference: -0.35
Gontero *et al.* [1261]	2008	21	Prospective	Golden Erect	at least 4 h/day for 6 months	45.7 ± 11.1	Flaccid length: 2.3 Stretched length: 1.7 Circumference: NR

NR = not reported.

9.3.1.3 Vacuum erection device

Vacuum erection devises (VED) are generally considered for patients who fail oral ED therapies [413, 1237]. In contrast, data regarding the use of VEDs on penile elongation is scarce. In a study with 27 men whose SPL was < 10 cm, the use of a VED three times a week for 20 minutes on each occasion, for six months, did not result in a significant increase in flaccid or SPL [1267]. On the other hand, the benefits of using a VED following PPI and RP have been demonstrated in the literature [1267-1272].

9.3.1.4 Endocrinological therapies

Testosterone administration has been used for a long time to increase the length of the penis in infant or pre-pubertal boys with micropenis. Topical administration of T or DHT has also been proposed by other authors with reported better outcomes with DHT, especially in poor responders to T or in those with type 2 alpha reductase deficiency [1273, 1274]. Finally, the possible use of the combination of hCG and FSH treatment has also been proposed with positive outcomes [1275, 1276]. Despite the treatment suggested it should be recognised that no face-to-face comparisons are available so far.

9.3.1.5 Summary of evidence and recommendations for the non-surgical management of short penile size

Summary of evidence	LE
Psychotherapy should not be undertaken in the realm of preventing individuals' legitimate choice to improve their lives. Conversely, psychotherapy is recommended when psychopathological comorbidities are detected, or when aversive relationship dynamics may underly the request for penile augmentation.	3
Cognitive behaviour therapy for BDD could be applied to cases of anxiety regarding penis size.	3
Penile traction therapy proved to be an effective treatment to achieve penile lengthening.	3
Vacuum erection devices proved to be an ineffective treatment in achieving penile lengthening.	3
Testosterone therapy, transdermal dihydrotestosterone and recombinant gonadotropins can restore penile size in boys with micropenis or disorders of sex development.	2b
Testosterone therapy does not increase penile size in adult men and in men with late-onset hypogonadism.	3

Recommendations	Strength rating
Consider psychotherapy when psychopathological comorbidities are detected, or when aversive relationship dynamics may underlie the request for penile augmentation.	Strong
Consider the use of penile traction therapy as a conservative treatment to increase penile length.	Weak
Do not use vacuum erection devices to increase penile length.	Weak
Use endocrinological therapies to restore penile size in boys with micropenis or disorders of sex development.	Strong
Do not use testosterone therapy or other hormonal therapies to increase penile size in men after puberty.	Strong

9.3.2 ***Surgical Treatments***

9.3.2.1 *Surgical treatment of adult acquired buried penis*

9.3.2.1.1 Adult acquired buried penis surgical procedures classification

According to the classification proposed by Pariser *et al.* different procedures may range from low complexity (including un-burying of penile shaft, reconstruction of penile shaft with the use of skin flaps or grafts, plastic surgical techniques to reconstruct the scrotum) to high complexity [including surgical removal of the suprapubic fat pad (escutcheonectomy) and operations to skin and subcutaneous fat layers of the abdominal wall (apronectomy] [1191].

The purpose of any surgical approach is to unbury the penile shaft, reconstruct genital teguments and eventually remove peri-genital or excess abdominal tissue in order to reduce the risk of recurrence. The goal is to balance an effective surgical procedure aiming to improve patient QoL, while minimising the incidence of postoperative complications. Lifestyle changes and risk factors modification, particularly weight loss, are widely considered as a proactive approach to minimise AABP surgical complications and should be encouraged before surgical intervention is undertaken. The broad spectrum of surgical interventions described to manage AABP is summarised in Table 25.

Table 25: Surgical interventions to manage adult acquired buried penis [1174]

Study	Year	n	Type of intervention (%)	Classification of intervention* (%)
Ngaage *et al.* [1180]	2021	15	3 (20%) abdominoplasty, 5 (33%) panniculectomy, 11 (73%) monsplasty, 3 (20) shaft reconstruction with scrotal flap, 7 (47%) STSG.	7 category II, 5 category IV, 3 category V
Kara *et al.* [1181]	2021	13	13 (100%) circumcision, penile liberation and STSG.	13 category II
Zhang *et al.* [1182]	2020	26	26 (100%) suprapubic liposuction and a modified Devine's technique.	26 category IV
Monn *et al.* [1183]	2020	67	53 (79.1%) split-thickness skin graft (STSG), 19 (28.4%) ligament fixation, 38 (56.7%) pubic lipectomy, 10 (14.9%) pubic liposuction, 17 (25.4%) abdominal panniculectomy, 16 (23.9%) urethroplasty.	-
Gao *et al.* [1184]	2020	32	32 (100%) suprapubic liposuction, suspensory ligament release and preputioplasty.	32 category IV
Aube *et al.* [1189]	2019	24	17 (70.8%) STSG, 17 (70.8%) penopubic ligament fixation, 17 (70.8%) pubic lipectomy, 9 (37.5%) abdominal panniculectomy, 3 (12.5%) pubic liposuction.	-
Cocci *et al.* [1190]	2019	47	(27.66%) circumcision, (19.14%) scrotoplasty, (4.25%) V-Y plasty of the pre-pubic region, (12.76%) thin STSG, (36.17%) thick STSG, (57.44%) suprapubic fat pad excision, (25.53%) abdominoplasty, (36.17%) division of the suspensory ligament.	-
Erpelding *et al.* [1185]	2019	16	2 (12.5%) penile liberation and STSG, 1 (6.2%) penile liberation, STSG, eschutcheonectomy and urethroplasty, 1 (6.2%) penile liberation, STSG and urethroplasty, 4 (25%) penile liberation, STSG, eschutcheonectomy and urethroplasty, 4 (25%) penile liberation, STSG, eschutcheonectomy and scrotoplasty, 4 (25%) penile liberation, STSG, eschutcheonectomy.	4 category II, 12 category IV

Hesse *et al.* [1186]	2019	27	27 (100%) Penile liberation, STSG, panniculectomy, abdominoplasty and monsplasty.	-
Zhang *et al.* [1187]	2019	15	15 (100%) suprapubic liposuction, penile suspensory ligament release and insertion of folded acellular dermal matrix between corpora cavernosa and pubis symphysis.	15 category IV
Monn *et al.* [1188]	2019	13	6 (46.2%) penile liberation, full thickness graft to the penis using the escutcheon tissue as a graft source, 7 (53.8%) penile liberation, panniculectomy, full thickness graft to the penis using the escutcheon tissue as a graft source.	6 category IV, 7 category V
Pariser *et al.* [1191]	2018	64	3 (5%) penile unburying with local skin flap, 17 (27%) skin graft to the shaft, 7 (11%) scrotal surgery (scrotectomy or scrotoplasty), 33 (52%) escutcheonectomy, 4 (6%) abdominal panniculectomy.	3 category I, 17 category II, 7 category III, 33 category IV, 4 category V
Theisen *et al.* [1192]	2018	16	16 (100%) escutcheonectomy, scrotectomy, and penile STSG.	16 category IV
Fuller *et al.* [1193]	2017	12	12 (100%) escutcheonectomy, scrotoplasty and penile STSG.	12 category IV
Voznesensky *et al.* [1194]	2017	12	11 (92%) debridement of penile skin and STSG to the penis, 12 (100%) escutcheonectomy, 10 (83%) abdominoplasty, 7 (59%) scrotoplasty, 12 (100%) securing the supra-penile dermis to the pubic dermal or periosteal tissue.	12 category IV/V
Hampson *et al.* [1177]	2017	42	42 (100%) limited suprapubic panniculectomy, radical excision of penile shaft skin and reconstruction with STSG and scrotoplasty if needed.	42 category IV
Ghanem *et al.* [1195]	2017	10	10 suprapubic liposuction.	10 category IV
Tausch *et al.* [1172]	2016	56	25 (45%) phalloplasty with or without a scrotal flap (if significant abdominal component panniculectomy to remove the excess suprapubic fat), 12 (21%) penile shaft reconstruction with STSG, 19 (34%) penile shaft reconstruction with STSG following excision of the involved tissues with any necessary adjunctive procedures.	-
Westerman *et al.* [1196]	2015	15	15 (100%) phalloplasty with ventral slit scrotal flap.	15 category II
Rybak *et al.* [1197]	2014	11	11 (100%) penile release, 10 (90.9%) STSG.	1 category I, 10 category II
Shaeer *et al.* [1198]	2009	64	64 (100%) adhesiolysis, suprapubic and lateral lipectomy, anchoring the penoscrotal and penopubic junctions, and skin coverage by a local flap.	64 category IV

The current evidence highlights the efficacy of AABP surgical treatment which has a low incidence of recurrence and satisfactory functional outcomes, as shown in Table 26, yet there is a significant incidence of post-operative complications (up to 3.5% of grade V according to Clavien-Dindo Classification) [1277].

Table 26: Surgical and functional outcomes of adult acquired buried penis repair [1174]

Study	Year	Overall post-operative complications	Recurrence of burying	Sexual outcomes	Urinary outcomes	Cosmetic outcomes
Ngaage *et al.* [1180]	2021	6 (44%)	2 (13%)	Spontaneous erections in 5 (83%)	7 (78%) voiding in standing position	-
Kara *et al.* [1181]	2021	4 (30%)	-	Increase in IIEF & SSS	-	All patients were pleased with the cosmetic outcome

Zhang *et al.* [1182]	2020	21 (80.8%)	-	-	-	Most patients had positive feedback toward their result of the operation, with a mean grade of 4.5+0.7.17 patients (65%) who were very satisfied with the outcome. Six patients (23%) were satisfied with the outcome. Three patients (12%) were neither satisfied nor dissatisfied with the outcome. None of the patients were dissatisfied nor very dissatisfied with the outcome
Monn *et al.* [1183]	2020	24 (57.1%)	-	33 (49.3%) patients with erection post-operatively	-	Satisfied 25 (37.3%); unsatisfied 9 (13.4%); neutral 33 (49.3%)
Gao *et al.* [1184]	2020	-	-	Increase in IIEF	-	-
Aube *et al.* [1189]	2019	15 (62.5%)	-	Good postoperative erection	-	Patient satisfaction in the case of a successful procedure was: 16 patients (76.2%) satisfied with the procedure, 5 patients (23.8%) neutral/not responding and no patients (0%) dissatisfied
Erpelding *et al.* [1185]	2019	3 (18.7%)	-	-	-	-
Hesse *et al.* [1186]	2019	15 (55.5%)	-	-	-	Nearly all patients (96%) reported early satisfaction with the procedure
Zhang *et al.* [1187]	2019	11 (73.3%)	-	No difficulty in sexual intercourse	None of the patients reported difficulty in urination	10 patients (66.7%) were very satisfied with the outcome, 4 patients (26.6%) were satisfied with the outcome, 1 patient (6.7%) was neither satisfied nor dissatisfied with the outcome, and no patient was dissatisfied with the appearance and function
Cocci *et al.* [1190]	2019	7 (14.9%)	-	Increase in IIEF of 3 points, vaginal penetration became possible in 97.87% of patients, erectile function improved in 42.55%, 48.93% needed to take PDE5i to enhance their nocturnal erections, improvement in penile erogenous sensation was recorded in 6.38%	-	-
Monn *et al.* [1188]	2019	5 (38.4%)	-	-	-	All patients reported subjective satisfaction with the cosmesis of their surgical outcome

Pariser *et al.* [1191]	2018	42 (65%)	-	-	-	-
Theisen *et al.* [1192]	2018	2 (10.5%)	1 (5.2%)	Significant improvement in 10 of 13 questions (77%)	Significant improvement in 10 of 12 questions (83%)	
Fuller *et al.* [1193]	2017	0 (0%)	-	-	-	-
Voznesensky *et al.* [1194]	2017	9 (75%)	9 (75%)	Improvement or the same degree of sexual activity (75%).	Improvement in urination (92%)	-
Ghanem *et al.* [1195]	2017	-	-	-	-	3 (30%) of the patients were very satisfied with the result, 5 (50%) patients were satisfied, 1 patient (10%) was neither satisfied nor dissatisfied, and 1 (10%) patient was dissatisfied. No patients were very dissatisfied.
Tausch *et al.* [1172]	2016	-	-	-	-	-

Summary of evidence	**LE**
Various surgical procedures may be considered to restore genital anatomy in adult acquired buried penis (AABP) patients.	3
Adult acquired buried surgery is burdened by a significant incidence of postoperative complications.	3
Lifestyle changes and risk factors modification, particularly weight loss, are widely considered as a proactive approach to minimise AABP surgical complications.	4
Adult acquired buried surgery may provide satisfactory functional outcomes with a low incidence of recurrence.	3

Recommendations	**Strength rating**
Extensively counsel patients on the benefits and complications of adult acquired buried penis (AABP) surgery.	Strong
Initiate lifestyle changes and modification of risk factors, particularly weight loss, to minimise AABP surgical complications and to optimise surgical outcomes.	Strong
Consider surgical treatment to address AABP.	Weak

9.3.2.2 Surgical treatment of congenital intrinsic penile shortness

Current literature reports a wide spectrum of possible surgical interventions aimed to address penile shortness. Nonetheless, the proposed spectrum of surgical interventions starts from less invasive procedures - such as suspensory ligament release (SLR) - to more complex genital reconstruction - such as total phallic reconstruction (TPR) [1278, 1279].

9.3.2.2.1 Suspensory ligament release (SLR)

This technique involves a surgical incision and SLR of the penis which attaches the penis to the pubic bone. The surgical access is via an infrapubic incision and may be combined with an elongating V-Y skin plasty [1279]. Several authors reported outcomes of SLR in the context of a congenital intrinsic penile shortness (Table 27).

Table 27: Suspensory ligament release [1278]

Author (year)	Year	n	Study design	Age, years	Follow-up, months	Stretched penile length gain, cm
Littara *et al.* [1280]	2019	21	Retrospective	38.08 ±1.1	12	1.1
Zhang *et al.* [1187]	2019	15	Retrospective	33.2 ± 4.6	3	4.3 ±1.6
Li *et al.* [1279]	2006	27	Retrospective	NR	16	1.1 ±1.1
Spyropoulos *et al.* [1250]	2005	11	Retrospective	25-25	Not reported	1.6 (1–2.3)

Measurements are expressed as median/mean, (IQR)/±SD.

9.3.2.2.2 Ventral phalloplasty/scrotoplasty

This intervention is based on a ventral shaft skin plasty to move the peno-scrotal angle proximally and increase the exposure of the penile shaft. A longitudinal incision or Z-plasty at the penoscrotal junction, securing the tunica albuginea to the proximal tunica dartos was performed by Xu *et al.* in 41 patients [1281]. The correction was successful in all patients with an improved median length of +2.1 cm in the flaccid state.

9.3.2.2.3 Suprapubic lipoplasty/liposuction/lipectomy

This intervention aims to reduce the thickness of the suprapubic fat pad either with a minimally invasive approach (liposuction) or surgically (lipectomy). The flattening of the suprapubic fat pad aims to increase penile shaft exposure.

Ghanem *et al.*, performed liposuction in ten patients using a 50-cc syringe with a 3- and 6-mm liposuction needle [1195]. The amount of fat removed ranged from 325 to 850 mL with a mean of 495.50 ± 155.39 mL. Three (30%) of the patients were very satisfied with the post-operative result, five (50%) patients were satisfied, one patient (10%) was neither satisfied nor dissatisfied, and one (10%) patient was dissatisfied. No patients were very dissatisfied. Shaeer's monsplasty technique was investigated in 20 patients [1282]. At three months post-operatively, the flaccid visible length was 7.1 ± 2.1cm, with a 57.9% improvement in length, and the erect visible length was 11.8 ± 2.1cm, with a 32% improvement in length. At final follow-up (eighteen months) a 73.1% improvement in satisfaction rate was detected.

9.3.2.2.4 Total phallic reconstruction (TPR)

This represents the most complex genital reconstruction possible, aiming to create a new phallus with a neo-urethra. The operation is reserved for severe penile insufficiency cases (e.g., congenital micropenis, exstrophy-epispadias complex) as the benefit should be balanced over possible complications [1278].

Lumen *et al.*, treated seven male patients (aged 15 to 42 years) with phalloplasty (6 with radial forearm free flap and 1 with anterolateral thigh flap) and implant surgery was offered approximately 1 year after the phallic reconstruction [1283]. There were no complications after surgical formation of the neophallus. Two complications were reported in the early post-operative period. Two patients developed urinary complications (stricture and/or fistula). Patient satisfaction after surgery was high in six cases and moderate in one case. Four patients underwent penile implant surgery and 50% were subsequently removed.

Perovic *et al.*, conducted TPR using musculocutaneous latissimus dorsi (MLD) in twelve patients [1284]. The mean (range) follow-up was 31 (6–74) months, and the penile size was 16 (14–18) cm long and 13 (11–15) cm in circumference. There was no flap loss or partial skin necrosis.

Garaffa *et al.*, reported a series of TPR using the radial artery forearm free flap in 16 patients with bladder/cloacal exstrophy and micropenis-epispadias complex [1285]. In one patient the distal third of the phallus was lost due to acute thrombosis of the arterial anastomosis immediately post-operatively. Almost all (93%) were fully satisfied in terms of cosmesis and size. Urethral stricture and fistula were the most common complications, which developed only at the native neourethral anastomosis. They were successfully managed by revision surgery. Sexual intercourse was achieved in 11 of the 12 patients who underwent PPI.

9.3.2.2.5 Summary of evidence and recommendations for surgical treatment of congenital intrinsic penile shortness

Summary of evidence	LE
Considering the wide spectrum and the complexity of surgical interventions aimed at addressing penile shortness, this surgery should be reserved to high volume centres.	4
Suspensory ligament release, ventral phalloplasty and suprapubic lipoplasty/liposuction/lipectomy provide an objective increase in penile length.	3
Suspensory ligament release, ventral phalloplasty and suprapubic lipoplasty/liposuction/lipectomy are associated with a significant incidence of complications.	3
Total phallic reconstruction provides satisfactory surgical and functional outcomes in men with micropenis.	3

Recommendations	Strength rating
Perform penile augmentation surgery in high-volume centres.	Strong
Use suspensory ligament release (SLR), ventral phalloplasty and suprapubic lipoplasty/ liposuction/lipectomy to address penile lengthening.	Weak
Extensively discuss possible complications related to suspensory ligament release, ventral phalloplasty and suprapubic lipoplasty/liposuction/lipectomy.	Strong
Use total phallic reconstruction to restore genital anatomy in patients affected by congenital micropenis.	Weak

9.3.2.3 Surgical treatment of acquired penile shortness

9.3.2.3.1 Penile prosthesis implantation (PPI)

The literature fails to show a direct relationship between PPI and penile length in men with ED and no concomitant PD. In a study by Deveci *et al.*, SPL was evaluated in men undergoing primary implant surgery due to diabetes or RP [1286]. Either three-piece (Alpha-1, Mentor, USA) and two-piece implants (Ambicor, AMS, Boston Scientific, USA) were used and most patients (72%) reported a subjective decrease in penile length, although no statistically significant difference was demonstrated in measured SPL [1286]. In another study, 45 patients with PD with no deformity or penile curvature < 30° or severe penile fibrosis/scarring were implanted with an AMS 700 LGX [1287]. The mean stretched penile length improved from 13.1 ± 1.2 cm to 13.7 ± 1.1 cm and 14.2 ± 1.2 cm at six and twelve months, respectively. A significant difference was also observed in the length of the stretched flaccid penis between six and twelve months [1287].

Some authors have evaluated the erect penile length following PPI. In a prospective study where patients with PD were excluded, erect penile length was compared from baseline achieved by intracavernosal injection and after PPI inflation. The authors demonstrated that there were 0.83 ± 0.25, 0.75 ± 0.20 and 0.74 ± 0.15 cm decreases in erect penile length six weeks, six months, and one year post-operatively, respectively [1288]. A study where patients with PD were excluded confirmed these results as the median pre-operative pharmacologically induced length (14.25 ± 2 cm) was decreased to median post-prosthesis penile length (13.5 ± 2.13 cm) [1289].

9.3.2.3.2 Penile disassembly

Penile disassembly has been described as a technique for penile lengthening [1290]. It consists of the separation of the penis into its anatomical components and the insertion of autologous cartilage in the space created between the glans cap and the tip of corpora cavernosa. Perovic *et al.*, in a study with 19 patients submitted to penile disassembly and implantation of autologous rib cartilage followed by VED therapy, reported an increase of 3 cm and 3.1 cm in SPL and erect length, respectively [1290]. The results of this surgery are poorly documented and significant complications such as glans necrosis can ensue.

9.3.2.3.3 Lengthening corporal manoeuvres

Penile length restoration with the use of the sliding technique (ST) and concomitant PPI was first described in a small series of three patients in 2012, and further supported by a larger series of 28-patient in a multi-centre study in 2015 [1110, 1114]. Although this technique is only used in cases of end-stage PD with severe shortening of the shaft, 95% of men were satisfied with their increase in length with an average penile lengthening of 3.2 cm (range, 2.5-4 cm). The modified sliding technique (MoST) and multiple slit technique (MuST) are further modifications of the original ST [1111, 1112]. In a series by Egydio *et al.*, 143 patients with

penile shortening and narrowing due to PD amongst other aetiologies underwent MoST or MuST procedures. The mean (range) penile length gain was 3.1 (2-7) cm at a median (range) follow-up of 9.7 (6-18) months [1111].

9.3.2.3.4 Total phallic reconstruction (TPR)

Radial forearm free flap is the most used reconstructive approach for TPR. In a single-centre study, Falcone *et al.*, reported their experience of ten patients who underwent TPR using RAFFF after traumatic penile loss [1291]. In six individuals, the urethral stump was sufficient for primary anastomosis and neourethra formation. The remaining patients had total penile avulsion and were voiding via a perineal urethrostomy. Consequently, a two-stage urethroplasty was necessary. Two patients developed an acute arterial thrombosis of the microsurgical anastomosis, which was successfully treated with emergency exploration. One patient had a neourethral stricture and fistula that required revision. All patients who underwent complete urethral repair were able to void and ejaculate through the phallus. After a median follow-up of 51 months, all patients were satisfied with the acquired size, cosmesis, and sensation. Six patients received a PPI and were able to also engage in penetrative intercourses. However, three patients had revision surgery (two due to infection and one due to mechanical failure) [1291].

9.3.2.3.5 Summary of evidence and recommendations for surgical treatment of acquired penile shortness

Summary of evidence	**LE**
Penile prosthesis implantation is not effective in increasing penile length.	3
The evidence for the use of penile disassembly manoeuvres and the lengthening corporal manoeuvres are limited.	3
Total phallic reconstruction yields to satisfactory outcomes despite the high incidence of post-operative complications.	3

Recommendations	**Strength rating**
Do not recommend penile prosthesis implantation, penile disassembly or lengthening corporal manoeuvres to patients seeking penile lengthening options.	Strong
Use total phallic reconstruction to restore genital anatomy in genetic males with penile inadequacy due to traumatic loss.	Weak

9.3.2.4 Penile girth enhancement

9.3.2.4.1 Penile Girth enhancement history

Nomograms were created for penile girth measurements, including flaccid penis circumference (n = 9407, 9.31 ± 0.90 cm) and erect circumference (n = 381, 11.66 ± 1.10 cm) [1136]. Unlike penile lengthening, there are no precise definitions or indications for penile girth enlargement in the literature or existing international guidelines [1292]. In recent years, men have increasingly approached urologists for penile girth enhancement to increase their self-confidence, to be cosmetically satisfied or to satisfy their partners [1293]. Current reports on penile girth enhancement techniques are from recent years [1293, 1294]. Although these surgical techniques are more and more frequently requested, the level of evidence for their use in clinical practice is low, notwithstanding the ethical considerations of surgery in this vulnerable group of patients.

9.3.2.4.2 Injection therapy

Injectable filling materials can be classified according to their different properties. They can be autologous, biological or synthetic. The fat injection material is obtained from the patient's own tissue (autologous), usually by liposuction (see the following surgical therapy section). Biological fillers can be of human and animal (collagen) or bacterial (Hyaluronic acid) origin. Poly-l-lactic acid (PLA), hydroxyethyl methacrylate, polyalkylimide hydrogel (PAAG), polymethylmethacrylate (PMMA), calcium hydroxyapatite (CHA), silicon and paraffin constitute filler materials of synthetic origin (Table 28) [1295].

Table 28: Origin of injectable filling materials

Autologous	Autologous fat tissue
Biological	Hyaluronic acid
Synthetic	Poly-l-lactic acid, hydroxyethyl methacrylate, polyacrylamide hydrogel, polymethylmethacrylate, calcium hydroxyapatite, silicon, paraffin

9.3.2.4.2.1 Soft tissue fillers (Hyaluronic acid and PMMA)

Hyaluronic acid

Injection of hyaluronic acid (HA) gel is one of the most commonly used injectable fillers in the field of plastic surgery [1237, 1296]. The application of HA for penile girth enhancement has recently gained increasing popularity due to its biocompatibility and infrequent mild temporary side effects. The newly invented cross-linked HA has a more lasting effect over time [1297]. Hyaluronic acid has been used for patients for penile girth enhancement. Studies have reported that an increase of 1.4 to 3.78 cm in penile girth is achieved with HA injection (Table 29). Patient satisfaction is high (78-100%) and no severe side effects have been reported [704, 1298-1301].

Table 29: Published data on evaluation of Hyaluronic acid injection therapy on penile girth enhancement

Author	Year	n	Study design	Age, years	Follow-up, months	Girth gain, cm	Complications, n (%)
Zhang *et al.* [1302]	2022	38	Retrospective	31.2 ± 6.7	12	2.44 ± 1.14	3 (7.9)
Ahn *et al.* [704]	2021	32	Multi-centre RCT	20-65	5-6	2.27± 1.26	2 (6.3)
Quan *et al.* [1303]	2021	230	Retrospective	30.34±5.23	6	1.80 ± 0.83	10 (4.3)
Yang *et al.* [1300]	2020	39	Multi-centre RT	19-65	5-6	2.1 ± 1.0	2 (5.13)
Yang *et al.* [1301]	2020	33	Multi-centre RT	20-66	18	1.41 ± 1.48	3 (9.1)
Yang *et al.* [1298]	2019	36	Multi-centre RT	20-65	11-12	1.69 ± 1.53	1 (2.78)
Kwak *et al.* [1299]	2011	50	Retrospective	42.5 (27-61)	18	3.78 ± 0.35	0 (0)
Summary		N/A	N/A	19-66	5-18	1.40 – 3.78	0-9.1

Measurements are expressed as median/mean, (IQR)/±SD.

Polymethylmethacrylate (PMMA)

Polymethylmethacrylate (PMMA) microspheres have been injected as a wrinkle filler. An average increase in penile circumference of 3.5 cm was reported in two studies using PMMA for penile girth enhancement [1304, 1305]. The authors reported that post-operative swelling and inflammatory reaction resolved within a few days and no pattern of PMMA microspheres migration to neighbouring regions was seen.

Poly-l-lactic acid

Poly-l-lactic acid (PLA) is another widely used soft tissue filler. Poly-l-lactic acid has enhanced effects by stimulating fibroblast proliferation and increasing collagen deposition in tissue. An average increase of 1.2 to 2.4 cm has been reported in the penile girth with PLA injection. No complications other than temporary local pain and swelling were reported in the treated patients [1298, 1306].

9.3.2.4.2.2 Other Fillers (silicone, paraffin)

Foreign body injections are still frequently practised in many countries (especially in East Asia and East Europe), either by the patient himself or by healthcare workers, using various substances such as paraffin, silicone or petroleum jelly (Vaseline), to increase the circumference of the penis [1307]. This results in a chronic granulomatous inflammatory foreign body reaction [1307, 1308]. The result of this practice is a pathological condition called sclerosing lipogranuloma of the penis also referred as paraffinoma or siliconoma according to the substance used [1307]. The resultant inflammatory process ranges from oedema and infection to Fournier's gangrene. Penile reconstructive surgeries may be required when siliconoma and paraffinoma require excision [1307-1313].

9.3.2.4.3 Surgical therapy

9.3.2.4.3.1 Autologous fat injection

This is a surgical technique based on thinning the lower abdomen with liposuction and injecting the harvested fat tissue into the penile shaft [1314-1317]. In retrospective studies, an average increase of 2 to 3.5 cm in penile circumference was reported in patients who underwent autologous fat injection. No statistically significant

decrease was observed in IIEF scores and no serious adverse events, such as penile abscess or deformity requiring reoperation occurred. Post-operative satisfaction survey showed that more than 75% of patients were satisfied (Table 30) [1280, 1314, 1315, 1318].

Table 30: Published data on the evaluation of autologous fat injection on penile girth enhancement

Author (year)	Year	n	Study design	Age (years)	Follow-up (months)	Girth gain (cm)	Complications, n (%)
Littara *et al.* [1280]	2019	334	Retrospective	36	12	2.76	49 (14.67)
Salem *et al.* [1318]	2019	15	Prospective	33 (23-45)	6	2-3.5	N/A
Kang *et al.* [1314]	2012	52	Retrospective	42.1	6	2.18-2.28	1 (1.92)
Panfilov *et al.* [1315]	2006	60	Retrospective	33.8	12	2.65	3 (5)
Summary	N/A	N/A	N/A	33-42.1	6-12	2-3.5	1.92-14.67

Measurements are expressed as median/mean, (IQR)/±SD.

9.3.2.4.3.2 Grafting procedures (albugineal and peri-cavernosal)
Until more rigorous multi-institutional studies reporting on complications and validated outcomes are known, penile girth enhancement procedures using grafts should be considered experimental (Table 31).

In a study of 69 patients using the porcine dermal acellular matrix graft (InteXen; American Medical Systems, Minnetonka, MN, USA) a 3.2 cm increase in flaccid state and 2.4 cm in erect state was reported at one year following surgery. The procedure was performed with an infrapubic incision, and 68 of 69 patients reported significant satisfaction using the Augmentation Phalloplasty Patient Selection and Satisfaction Inventory. Graft fibrosis has been observed in up to 13% of patients, and a mean reduction in penile length of 0.5 cm has been reported in patients with fibrosis [1319].

Techniques using venous grafts for penile girth enhancement have also been described [1320]. Initial results are encouraging, but better designed RCTs are needed.

Dermal fat grafts are free only grafts composed of deepithelialized dermis and subcutaneous fat. An area of approximately 10 x 5 cm is required for graft harvesting. An increase in penile girth of 1.67 to 2.3 cm has been reported in studies with the dermal fat graft technique. Penile oedema up to 27%, painful erection up to 27%, and curvature due to graft fibrosis up to 9% have been reported. Side effects such as penile hypoesthesia, skin necrosis, and infection were not reported [1250, 1321, 1322].

Table 31: Published data on evaluation of grafting techniques on penile girth enhancement

Author (year)	Year	n	Study design	Technique	Age, years	Follow up (months)	Girth gain (cm)	Complications, n (%)
Zhang *et al.* [1324]	2016	30	Retrospective	Dermal graft	23.7 (19-35)	13	1.5	1 (3.3)
Xu *et al.* [1322]	2016	23	Retrospective	SLR + skin advancement + dermal fat graft	23 (18-33)	6	1.67	7 (30.43)
Tealab *et al.* [1325]	2013	18	Retrospective	Acellular collagen matrix graft	24 (19-38)	12	2.3	8 (44.44)
Mertziatis *et al.* [1321]	2013	82	Retrospective	SLR + skin advancement + Dermal fat graft	24	12	2.2	25 (31.64)
Spyropoulos *et al.* [1250]	2005	4	Retrospective	SLR + Dermal fat graft	32	14	2.3	No major complication

Alei *et al.* [1319]	2012	69	Retrospective	Porcine dermal acellular matrix graft	28.2 (19-59)	12	Flaccid: 3.2; Erect: 2.4	19 (27.5)
Austoni *et al.* [1320]	2002	39	Retrospective	Corporal venous graft	24-47	9	Flaccid: no change, Erect: 2.9	1 (2.56)
Summary	N/A	N/A	N/A	N/A	18-68	6-48	0-4.9	0-44.44%

9.3.2.4.3.3 Biodegradable scaffolds

This is a technique based on using fibroblasts (harvested from patients' own scrotum skin and dartos tissue) in tissue cultures and seeding them in microporous biodegradable poly-lacti-co-glycolic acid (PLGA) scaffolds and implanting these scaffolds between Dartos and Buck's fascia. A limited number of studies have reported girth gain of up to 4.02 cm with implantation of biodegradable scaffolds [1326-1328] (Table 32).

Table 32: Published data on the evaluation of implantation of biodegradable scaffolds

Author	Year	n	Study design	Age (years)	Follow up (months)	Girth gain (cm)	Complications, n (%)
Djordjevic *et al.* [1326]	2018	21	Retrospective	28 (22-37)	38 (13-66)	Flaccid: 1.1 ± 0.4; Erect: 1±0.3	2 (9.52)
Jin *et al.* [1327]	2011	69	Multi-centre non-controlled	33±9.14	6	Flaccid: 4.01; Erect: 4.02	6 (8.69)
Perovic *et al.* [1328]	2006	84	Multi-centre prospective non-controlled	28.77±6.61	24.67	Flaccid: 3.35; Erect: 2.47	8 (9.52)
Summary	N/A	N/A	N/A	18-60	6-60	1-4.02	8.69-9.52%

9.3.2.4.3.4 Subcutaneous penile implant (Penuma®)

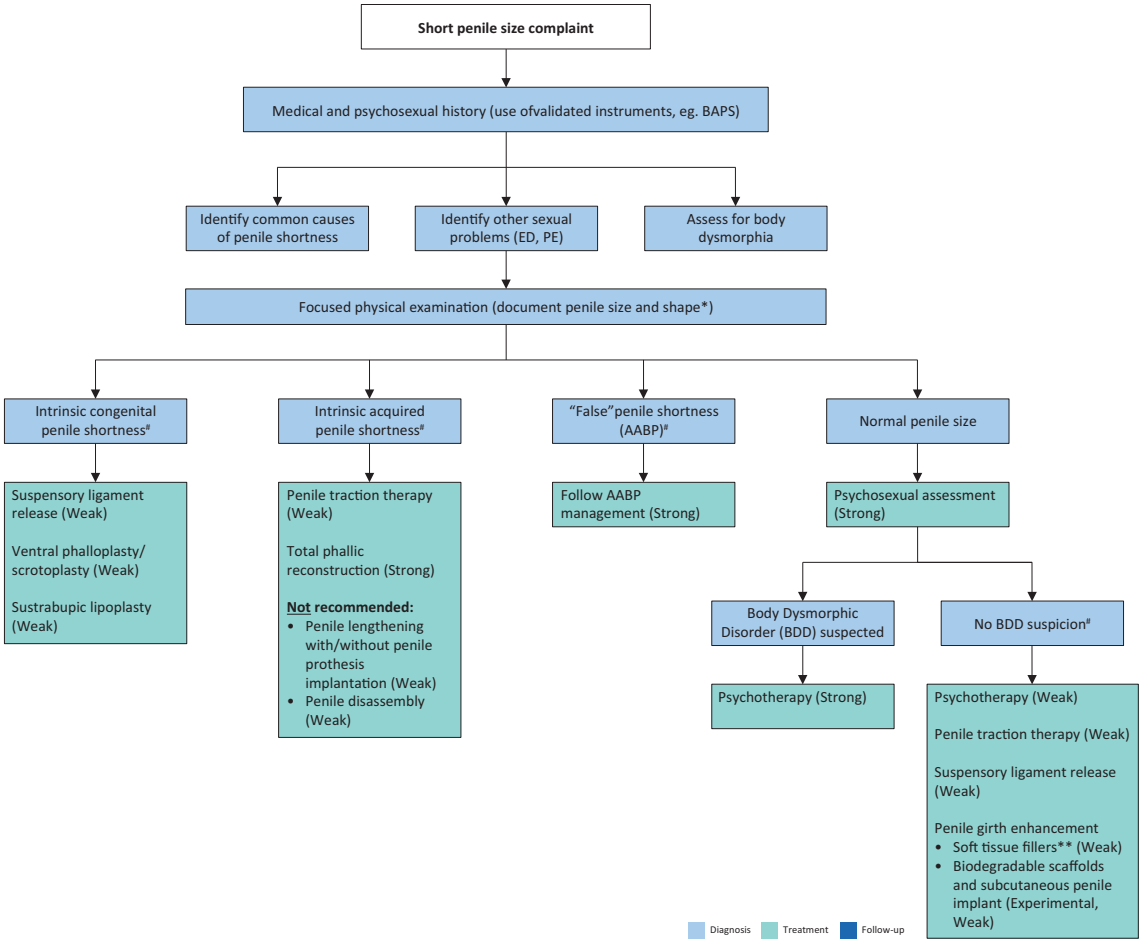
Recently, a silicone penile implant called "Penuma®" (International Medical Devices [Beverly Hills, CA, USA]) has been approved and has shown promising results for penile girth enhancement. Penuma® is a soft silicone subcutaneous implant placed on 3/4 of the penile shaft and fixed to the glans with a polyester mesh [1323]. Studies have reported an average increase in penile circumference of 2 to 5 cm with Penuma® insertion. According to published data complication rates (usually mild and transient, occur in <5%) and the removal rate (1%) of the implant has been reported to be relatively low [1323, 1329].

9.3.2.4.4 Summary of evidence and recommendations for penile girth enhancement

Summary of evidence	LE
Various surgical approaches with specific outcomes and complications have been considered to address penile girth enhancement, with limited benefit.	3
Hyaluronic acid (HA), Poly-l-lactic acid (PLA), hydroxyethyl methacrylate, polyacrylamide hydrogel (PAAG), polymethylmethacrylate (PMMA), calcium hydroxyapatite are used as injectable materials for penile girth enhancement.	3
Patient satisfaction with soft tissue fillers (especially HA, PMMA and PLA) is high (> 78%).	3
No complications other than temporary local pain and swelling were reported in patients treated with soft tissue fillers.	3
Using silicone, paraffin and petroleum jelly (Vaseline) in penile girth enhancement causes a range of complications ranging from oedema up to infection to Fournier's gangrene.	3
Not enough long term data are available on autologous fat injection for penile girth enhancement.	4
Not enough long term data are available on grafting procedures (dermal acellular matrix graft, venous grafts or dermal fat grafts).	4
Grafting procedures are associated with high complication rate and low rate of patient's satisfaction.	3
Not enough long term data are available on biodegradable scaffolds and subcutaneous penile implant (Penuma®) .	4

Recommendations	Strength rating
Counsel patients extensively regarding the risks and benefits of penile girth enhancement techniques.	Strong
Do not use silicone, paraffin and petroleum jelly (Vaseline) to address penile girth enhancement.	Strong
Use hyaluronic acid, soft tissue fillers and autologous fat injection to address penile girth enhancement.	Weak
Do not use hyaluronic acid, soft tissue fillers and autologous fat injection to address penile girth enhancement in men with penile dysmorphic disorder.	Weak
Do not use grafts in penile girth enhancement as they are considered experimental.	Strong
Do not use biodegradable scaffolds and subcutaneous penile implant (Penuma®) to address penile girth enhancement as experimental.	Strong

Figure 11: Management of short penile size



** Penile length should be measured stretched both from the penopubic skin junction-to-glans tip (STT) and from the pubic bone-to-glans tip (BTT).*

 # There is a lack of evidence to recommend one treatment over another.

***Hyaluronic acid (HA), poly-l-lactic acid (PLA), hydroxyethyl methacrylate, polymethylmethacrylate (PMMA), polyacrylamide hydrogel (PAAG) and calcium hydroxyapatite are considered as injectable materials for penile girth enhancement. Although the level of evidence is low, there is more evidence for HA, PLA and PMMA. Do not use silicone, paraffin or Vaseline (Strong evidence against).*

The strength of recommendations is depicted between brackets where appropriate.

9.3.2.5 Functional outcomes: sexual function, sensitivity, impact on quality of life and emotional adjustment

Cosmetic treatments, including surgery, help to restore self-esteem, reduce anxiety, social phobia, and depressive mood states regarding body concerns, and increase individuals' well-being and QoL [1123, 1124]. Therefore, we can expect men with genuine short penis to use available resources to adjust the length or girth of their penis as a mean to improve their sense of identity and fit cultural standards regarding penile size and function. Currently, the results of penile augmentation techniques seem mixed. The utilization of fillers led to enhanced genital self-image and self-esteem, as well as reduced symptoms of PDD. However, no effects were observed in terms of self-confidence or satisfaction with sexual relationship [1257]. Likewise, penile lengthening or girth enhancement surgery seem to result in poor satisfaction, poor erectile function and sensitivity in men with normal penis size [1134]. Despite those negative outcomes, cases of increased satisfaction have been registered [1330]. Male genital self-image has been related to IIEF domains: sexual desire, orgasmic and erectile function, intercourse and overall satisfaction [1247]. Similarly, perceived penis size seems to predict erectile function more than objective size [1130]. In addition, reduced penetrative and receptive oral sex is associated with men's dissatisfaction regarding their penis [1331]. For these reasons, more efforts should be made in order to clarify the impact of penile augmentation treatments on men's and partners' well-being and QoL. As for men with BDD, they have shown reduced erectile and orgasmic function, as well as less intercourse satisfaction as compared with controls, while men with SPA revealed reduced satisfaction. Sexual desire seemed untouched in BDD and SPA cases [1257, 1332].

9.3.2.6 Final remarks

The complaint of "short penis" is variable in presentation and aetiology. Some patients demonstrate anatomical and pathological conditions while others do not. A vast array of treatments for different aetiologies of "short penis," both surgical and non-surgical, have been reviewed. If psychopathological symptoms are detected, the patient must be referred for further medical diagnosis. Treatment for short-penis syndrome requires a multi-disciplinary approach, including medical and ethical considerations, and the majority of reported outcomes are based on a paucity of evidence.

10. PRIAPISM

Priapism is a persistent or prolonged erection in the absence of sexual stimulation that fails to subside. It can be divided into ischaemic, non-ischaemic and stuttering priapism. The guidelines are based on three systematic reviews addressing the medical and surgical management of ischaemic and non-ischaemic priapism and the overall management of priapism related to sickle cell disease [1333-1335].

10.1 Ischaemic (Low-Flow or Veno-Occlusive) Priapism

10.1.1 Epidemiology, aetiology, pathophysiology and Diagnosis

Ischaemic priapism is a persistent erection marked by rigidity of the corpora cavernosa and by little or no cavernous arterial inflow [1336]. Ischaemic priapism is the most common subtype of priapism, accounting for > 95% of all episodes [1336, 1337]. In ischaemic priapism, there are time-dependent metabolic alterations within the corpus cavernosum progressively leading to hypoxia, hypercapnia, glucopenia and acidosis [1338, 1339].

Ischaemic priapism that lasts beyond 4 hours is similar to a compartment syndrome and characterised by the development of ischaemia within the closed space of the corpora cavernosa, which severely compromises the cavernosal circulation. Emergency medical intervention is required to minimise irreversible consequences, such as smooth muscle necrosis, corporal fibrosis and the development of permanent erectile dysfunction (ED) [1340, 1341]. The duration of ischaemic priapism represents the most significant predictor for irreversible consequences, thus including ED. In this context, interventions beyond 48-72 hours of onset may help to relieve the erection and pain, but have little clinical benefit in preventing long-term ED [1342].

No specific pathophysiological causes of ischaemic priapism can be identified in most cases [1336, 1343], although the common aetiological factors include sickle cell disease (SCD), haematological dyscrasias, neoplastic syndromes, and several pharmacological agents (e.g., intracavernosal PGE1 therapy) (Table 33). Ischaemic priapism may occur (0.4-35%) after intracavernosal injection of erectogenic agents [1336, 1340, 1344-1346]. The risk is higher with papaverine-based combinations [1347], while the risk of priapism is < 1% following prostaglandin E1 injection [1348].

Second-generation antipsychotics (33.8%), other medications (11.3%), and alpha-adrenergic antagonists (8.8%) accounted for the greatest percentage of published drug-induced priapism cases [1349]. Isolated cases of priapism have been described in men who have taken PDE5Is [1336]. Data from the FDA Adverse Reporting System Public Dashboard showed that PDE5Is-induced priapism accounted for only 2.9% of drug-induced priapism. However, most of these men also had other risk factors for priapism, and it is unclear whether PDE5Is *per se* can cause ischaemic priapism [1336, 1350]. Since most men who experience priapism following PDE5I treatment have additional risk factors for ischaemic priapism, PDE5Is use is usually not regarded as a risk factor in itself. In terms of haemoglobinopathies, SCD is the most common cause of priapism in childhood, accounting for 63% of cases. It is the primary aetiology in 23% of adult cases [1348].

Mechanisms of SCD-associated priapism may involve derangements of several signalling pathways in the penis [1351]. Contrary to traditional belief, maintenance of physiological testosterone levels does not cause priapism, but rather preserves penile homeostasis and promotes normal erectile function [1352, 1353]. Testosterone deficiency is considered a controversial risk factor: it is prevalent in patients with SCD, but recent evidence indicates that it may not be a risk factor for priapism [1354].

Priapism resulting from metastatic or regional infiltration by tumour is rare and usually reflects an infiltrative process, more often involving the bladder and prostate as the primary cancer sites [1355]. In a large retrospective study including 412 men with ischaemic priapism, eleven (3.5%) had malignant priapism, of which seven cases were a consequence of local invasion while the others were secondary to haematological malignancy [1356]. The conventional therapeutic recommendations for pharmacological treatment are unlikely to be effective and all of these men should have MRI of the penis and be offered supportive care and medical intervention for their primary cancer. In selected cases where palliative treatment options fail to control penile pain, a palliative penectomy can be considered.

Partial priapism, or idiopathic partial segmental thrombosis of the corpus cavemosum, is a rare condition. It is often classified as a subtype of priapism limited to a single crura without ischaemia, but rather a thrombus is present within the corpus cavernosum. Its aetiology is unknown, but bicycle riding, trauma, drug use, sexual intercourse, haematological diseases and α-blocker intake have all been associated with partial segmental thrombosis [1357]. The presence of a congenital web within the corpora is also a risk factor [1358].

Table 33: Aetiological factors for the development of priapism

Idiopathic
-
Haematological dyscrasias, vascular and other disorders
• SCD • thalassemia • leukaemia • multiple myeloma • haemoglobin Olmsted variant • fat emboli during hyperalimentation • haemodialysis • glucose-6-phosphate dehydrogenase deficiency • factor V Leiden mutation • vessel vasculitis • (e.g., Henoch-Schönlein purpura; Behçet's disease; anti-phospholipid antibodies syndrome)
Infections (toxin-mediated)
• scorpion sting • spider bite • rabies
Metabolic disorders
• amyloidosis • Fabry's disease • gout

Neurogenic disorders
• 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)
• prostate • urethra • testis • bladder • rectal • lung, kidney
Medications
• Vasoactive erectile agents (i.e., papaverine, phentolamine, prostaglandin E1/alprostadil, combination of intracavernous therapies) • α-adrenergic receptor antagonists (i.e., prazosin, terazosin, doxazosin and tamsulosin) • Anti-anxiety agents (hydroxyzine) • Anticoagulants (heparin and warfarin) • Antidepressants and antipsychotics (i.e., trazodone, bupropion, fluoxetine, sertraline, lithium, clozapine, risperidone, olanzapine, chlorpromazine, thioridazine, phenothiazines and methylphenidate) • Antihypertensives (i.e., hydralazine, guanethidine and propranolol) • Hormones (i.e., gonadotropin-releasing hormone and testosterone) • Recreational drugs (i.e., alcohol, marijuana, cocaine [intranasal and topical], and crack, cocaine)

10.1.1.1 Summary of evidence on the epidemiology, aetiology and pathophysiology of ischaemic priapism

Summary of evidence	LE
Ischaemic priapism is the most common type, accounting for more than 95% of all cases.	1b
Ischaemic priapism is identified as idiopathic in most patients, while sickle cell disease is the most common cause in childhood.	1b
Ischaemic priapism occurs relatively often (about 5%) 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 Phosphodiesterase Type 5 Inhibitors, with only sporadic cases reported.	4

10.1.2 ***Diagnostic evaluation***

10.1.2.1 History

Taking a comprehensive history is critical in priapism diagnosis and treatment [1336, 1359]. The medical history must specifically enquire about SCD or any other haematological abnormality [1360, 1361] and a history of pelvic, genital or perineal trauma. The sexual history must include the duration of the erection; the presence and degree of pain; prior drug treatment and recreational drug use; history of priapism and methods of treatment; and erectile function prior to the last priapism episode [1336]. The history can help to determine the underlying priapism subtype (Table 34). Ischaemic priapism is classically associated with progressive penile pain and the erection is rigid. Conversely, non-ischaemic priapism is often painless and the erections often fluctuate in rigidity.

Table 34: Key findings in priapism (adapted from Broderick *et al.* [1336])

	Ischaemic priapism	Non-ischaemic priapism
Corpora cavernosa fully rigid	Typically	Seldom
Penile pain	Typically	Seldom
Abnormal penile blood gas	Typically	Seldom
Haematological abnormalities	Sometimes	Seldom
Recent intracavernosal injection	Sometimes	Sometimes
Perineal trauma	Seldom	Typically

10.1.2.2 Physical examination

In ischaemic priapism, the corpora are fully rigid and tender, but the glans penis is soft. The patient usually complains of severe pain. Pelvic examination may reveal an underlying pelvic or genitourinary malignancy [1356].

10.1.2.3 Laboratory testing

Laboratory testing should include a complete blood count, white blood cell count with blood cell differential, platelet count and coagulation profile to assess anaemia and detect haematological abnormalities [1336, 1359].

Aspiration of blood from the corpora cavernosa is compulsory as an entry level investigation. It usually reveals dark ischaemic blood. Blood gas analysis is essential to differentiate between ischaemic and non-ischaemic priapism (Table 34). Further laboratory testing should be directed by the history, clinical examination and laboratory findings. These may include specific tests (e.g., haemoglobin electrophoresis) for diagnosis of SCD or other haemoglobinopathies.

10.1.2.4 Penile imaging

Colour Doppler US of the penis and perineum is recommended after clinical diagnosis and can differentiate ischaemic from non-ischaemic priapism as an alternative or adjunct to blood gas analysis (Figure 12) [1362-1365]. Colour Doppler US can identify the presence of the fistula as a blush with 100% sensitivity and 73% specificity [1364].

Ultrasound of the penis should be performed before corporal blood aspiration in ischaemic priapism to prevent aberrant blood flow which can mimic a non-ischaemic or reperfusion picture after intervention for low-flow priapism [1366].

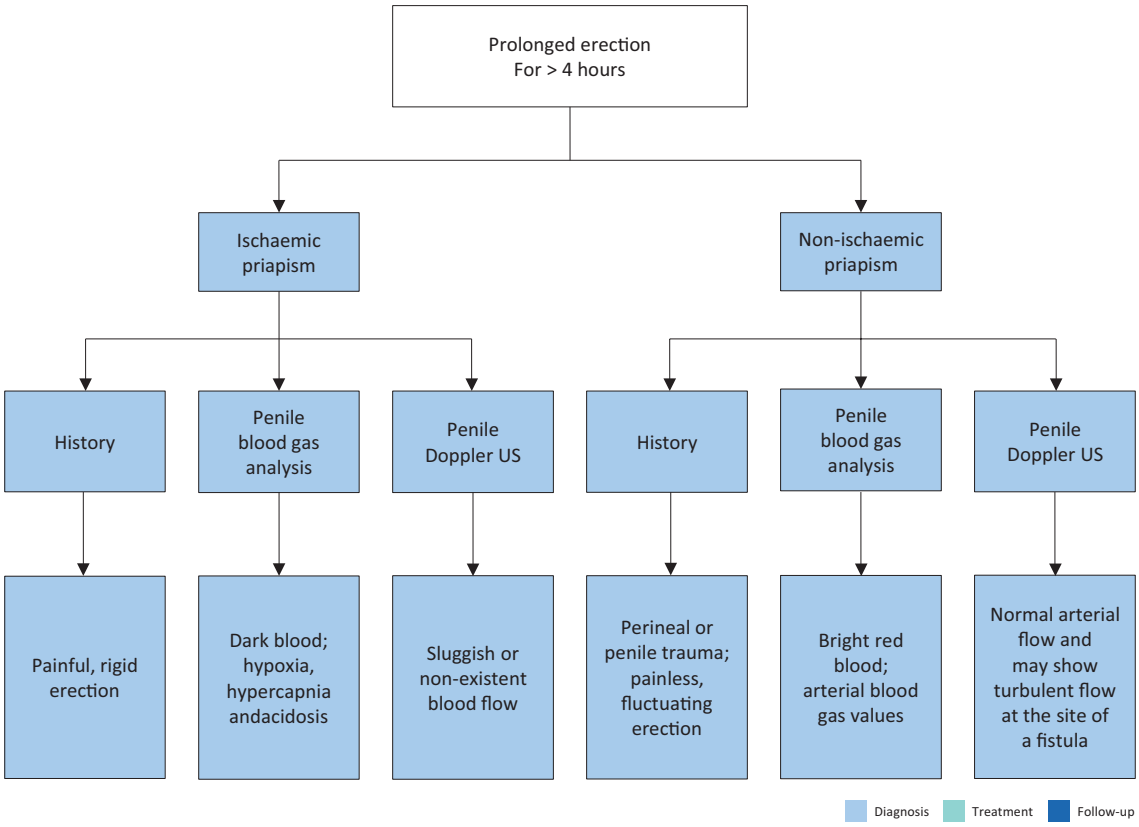
Penile MRI can be used in the diagnostic evaluation of priapism and may be helpful in selected cases of ischaemic priapism to assess the viability of the corpora cavernosa and the presence of penile fibrosis. In cases of refractory priapism or delayed presentation (> 48 hours), smooth muscle viability can be indirectly assessed. In a prospective study of 38 patients with ischaemic priapism, the sensitivity of MRI in predicting non-viable smooth muscle was 100%, when correlated with corpus cavernosum biopsies [1366]. All patients with viable smooth muscle on MRI maintained erectile function on clinical follow-up with the non-viable group being offered early prosthesis.

Table 34: Typical blood gas values (adapted from Broderick *et al.* [1336])

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

pCO_2 partial pressure of carbon dioxide; pO_2 partial pressure of oxygen

Figure 12: Differential diagnosis of priapism



10.1.2.5 Summary of evidence and recommendations for the diagnosis of ischaemic priapism

Summary of evidence	LE
Medical history including the assessment of known haematological abnormalities (e.g., SCD), history of pelvic/perineal/genital trauma, prior drug treatment or recreational drug use is essential to identify the possible a etiology and the type of priapism	3
Blood gas analysis performed before blood aspiration from the corpora can differentiate between ischaemic and non-ischaemic priapism. A full blood count and haemoglobinopathy screen could reveal haematological alterations.	3
Penile Colour Doppler US can differentiate from ischaemic and non-ischaemic priapism when performed before corporal blood aspiration.	3
Penile MRI can predict non-viable smooth muscle in patients with ischaemic priapism.	3

Recommendations	Strength rating
Take a comprehensive history to establish the diagnosis which can help to determine the priapism subtype.	Strong
Include a physical examination of the genitalia, perineum and abdomen in the diagnostic evaluation.	Strong
Include a full blood count, white blood cell count with blood cell differential, platelet count and coagulation profile. Directed further laboratory testing should be performed depending upon the history and clinical and laboratory findings. In children with priapism, perform a complete evaluation of all possible causes.	Strong
Perform a haemoglobinopathy screen in patients with low flow priapism who are at high risk of sickle cell disease or thalassemia.	Strong
Analyse the blood gas parameters from blood aspirated from the penis to differentiate between ischaemic and non-ischaemic priapism.	Strong

Perform colour duplex ultrasound of the penis and perineum before aspiration to differentiate between ischaemic and non-ischaemic priapism.	Strong
Use magnetic resonance imaging of the penis in cases of prolonged ischaemic priapism or refractory priapism, as an adjunct to predict smooth muscle viability.	Weak

10.1.3 ***Disease management***

Acute ischaemic priapism is a medical emergency. Urgent intervention is mandatory and should follow a stepwise approach. The aim of any treatment is to restore penile detumescence, without pain, in order to prevent corporal smooth muscle fibrosis and subsequent ED.

10.1.3.1 Medical Management – first-line treatment

First-line medical treatments for ischaemic priapism of more than 4 hours duration are strongly recommended before any surgical treatment. Conversely, first-line treatments initiated beyond 48 hours, while relieving priapism, have little documented benefit in terms of long-term erectile function preservation. This is likely to be the consequence of irreversible smooth muscle hypoxia and damage that begins to be established by approximately 48 hours of the onset of ischaemia [1340-1342]. It has been shown in a series of 50 patients with low-flow priapism who were successfully treated and followed-up for a mean of 66 months, that those with priapism lasting for more than 48 hours had a significant risk of ED [1340].

Historically, several first-line treatments have been described including exercise, ejaculation, ice packs, cold baths, and cold water enemas [1336]. However, there is limited evidence for the benefit of these measures and they may even exacerbate the condition in SCD patients. Success rates for these conservative measures alone have rarely been reported. In a small series, cold water enemas have been reported to induce detumescence in six out of ten cases [1367]. In another study 24.5% of 122 patients achieved detumescence following priapic episodes lasting for more than 6 hours by cooling of the penis and perineum, and walking upstairs [1368].

10.1.3.1.1 Penile anaesthesia/analgesia

Blood aspiration and intracavernous injection of a sympathomimetic agent can be performed without any anaesthesia; however, anaesthesia may be necessary when there is severe penile pain. Whilst anaesthesia may not alleviate the ischaemic pain, cutaneous anaesthesia facilitates 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).

10.1.3.1.2 Aspiration ± irrigation with 0.9% w/v saline solution

The first intervention for an episode of priapism lasting more than 4 hours consists of corporal blood aspiration to drain the stagnant blood from the corporal bodies, making it possible to relieve the compartment-syndrome-like condition within the corpus cavernosum. Blood aspiration may be performed with intracorporeal access either through the glans or via percutaneous needle access to the lateral aspect of the proximal penile shaft, using a 16 or 18 G angio-catheter or butterfly needle. The needle must penetrate the skin, the subcutaneous tissue and the tunica albuginea to drain blood from the corpus cavernosum .

Some clinicians advocate using two angiocatheters or butterfly needles at the same time to accelerate drainage, as well as aspirating and irrigating simultaneously with a saline solution [1368]. Aspiration should be continued until bright red, oxygenated blood is aspirated.

Several case series have reported outcomes for first-line treatments; however, in most cases, aspiration and irrigation were combined with intracavernosal injection of sympathomimetic agents [1334], thus making it difficult to draw conclude the success rate of aspiration + irrigation
alone [1334]. Overall, case series and retrospective studies reported a success rate ranging from 0 to 100% of cases [1334]. In an RCT, 70 patients with ischaemic priapism lasting more than 6 hours secondary to intracavernosal injection were treated with aspiration plus saline irrigation at different temperatures [1368]. The study reported an 85% success rate with the optimum results achieved using a 10°C saline infusion after blood aspiration.

There is insufficient data to determine whether aspiration followed by saline intracorporeal irrigation is more effective than aspiration alone.

10.1.3.1.3 Aspiration ± irrigation with 0.9% w/v saline solution in combination with intracavernous injection of pharmacological agents.

This combination is currently considered the standard of care for the treatment of ischaemic priapism [1336, 1369, 1370]. Pharmacological agents include sympathomimetic drugs or α-adrenergic agonists. Intracavernous sympathomimetic agents include phenylephrine, etilephrine, ephedrine, epinephrine, norepinephrine and metaraminol with a resolution rate of up to 80% [1336, 1369, 1371-1378]. The use of intracavernous adrenaline injection alone has also been sporadically reported [1379]. It has been reported that the use of a sympathomimetic agent combined with prior intracavernosal aspiration or irrigation had a resolution ranging from 80 to 100% of cases as compared with 58% in those who had a sympathomimetic injection alone [1334, 1370].

The potential treatment-related adverse effects of intracavernous phenylephrine (and other sympathomimetic agents) include headache, dizziness, hypertension, reflex bradycardia, tachycardia and palpitations and sporadic subarachnoid haemorrhage [347]. Monitoring of blood pressure and pulse should be performed during intracavernous administration of sympathomimetic agents. As intracavernous sympathomimetic agents can cause hypertension, the Guidelines Panel is of the opinion that these agents are contraindicated in patients with malignant or poorly controlled hypertension, as there are case reports of significant cardiovascular and neurological complications following the use of these pharmacological agents for priapism [1372, 1380, 1381]. Similarly, data suggest that sympathomimetic agents cause a hypertensive crisis when given with monoamine oxidase inhibitors, hence these medications should not be used together [1382].

10.1.3.1.4 Intracavernosal and oral pharmacological agents

Pharmacological agents for the treatment of priapism are discussed in more detail in the following section. Table 35 summarises dosing and administration of these agents.

- *Phenylephrine*

Phenylephrine is a selective α-1-adrenergic receptor agonist that has been observed in small case series to be effective at producing detumescence in priapism, when given as an intracavernosal injection, with few adverse effects [1377, 1383]. Phenylephrine is the recommended adrenergic agonist drug of choice due to its high selectivity for the α-1-adrenergic receptor, without concomitant β-mediated inotropic and chronotropic cardiac effects [1371, 1375, 1376].

Phenylephrine has potential cardiovascular adverse effects [1336, 1369, 1371, 1372, 1375, 1376] and it is recommended that blood pressure and pulse are monitored every fifteen minutes for one hour after injection. This is particularly important in older men with pre-existing cardiovascular diseases. After injection, the puncture site should be compressed and the corpus cavernosum massaged to facilitate drug distribution.

- *Etilephrine*

Etilephrine is also an adrenergic agonist that directly stimulates both α and β adrenergic receptors [1370]. Most of the literature describing the use of etilephrine for treatment of priapism is related to men with SCD but there are small retrospective case series that have reported its benefits for priapism secondary to iatrogenic causes [1384, 1385]. Etilephrine is the second most widely used sympathomimetic agent [1372].

- *Methylene blue*

Methylene blue is a guanylate cyclase inhibitor, that may be a potential inhibitor of endothelial-mediated cavernous smooth muscle relaxation. Small retrospective case series have reported its successful use for treating short-term pharmacologically-induced priapism [1386, 1387]. Treatment-related adverse effects include a transient burning sensation and blue discolouration of the penis.

- *Adrenaline*

Adrenaline produces both α-adrenergic receptor agonist and β-adrenergic receptor activity. Intracavernosal adrenaline has been used in patients with ischaemic priapism due to an intracavernous injection of vasoactive agents. The limited literature [1379, 1388] suggests that adrenaline can achieve detumescence in short-term priapism, with one small case series reporting a success rate of over 50% after a single injection, with an overall success rate of 95% with repeated injections [1379, 1388].

- *β-2-agonists*

Oral terbutaline is a β-2-agonist with minor β-1 effects and some α-agonist activity; although its mechanism of action is not yet fully understood [1389-1391]. The main use of terbutaline is for prevention of recurrent episodes of prolonged erection. Oral treatment with terbutaline was tested in three placebo-controlled RCTs

[1390-1392] showing a success rate of 30 to 60% in patients with ischemic priapism associated with intracavernous injection of erectogenic agents. Terbutaline should be given cautiously in patients with coronary artery disease, increased intravascular fluid volume, oedema or hypokalaemia [1391]. In a single multi-centre prospective study, another β-2-agonist, salbutamol, has been reported to induce detumescence in 34% of cases of prolonged erection (more than three hours) after intracavernous injection of erectogenic agents [1393]. However, more robust data are needed to recommend oral salbutamol for the treatment of ischaemic priapism.

Table 35: Medical treatment of ischaemic priapism

Drug	Dose/Instructions for use
Phenylephrine	• Intracavernous injection of 200 µg every 3-5 minutes. • Maximum dosage is 1 mg within 1 hour. • Lower doses are recommended in children and patients with severe cardiovascular diseases.
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 is compressed for an additional 5 minutes.
Adrenaline	• Intracavernous injection of 2 mL of 1/100,000 adrenaline solution up to five times over 20 minutes.
Terbutaline	• Oral administration of 5 mg for priapism lasting more than 2.5 hours, after intracavernous injection of vasoactive agents.

10.1.3.1.5 Management of priapism related to sickle cell disease

The results of a systematic review on the overall management of priapism related to SCD found that few studies were conducted exclusively on patients with SCD and studies on mixed populations usually did not report separate data on SCD patients [1335]. Clear and systematic reporting of patient characteristics, interventions and outcomes was lacking, and the length of follow-up, if reported, varied significantly among the studies. Overall, the quality of studies was deemed poor to allow high-quality, evidence-based recommendations to be made.

Urgent intervention is essential and the general approach is similar to that described for other cases of ischaemic priapism and should be co-ordinated with a haematologist [1394-1396].

However, as with other haematological disorders, other therapeutic interventions may also need to be implemented [1394, 1396, 1397]. Specific measures for SCD-related priapism include intravenous hydration and narcotic analgesia while preparing the patient for aspiration and irrigation. Additionally, supplemental oxygen administration and alkalinisation with bicarbonate can be helpful [1395].

Haemoglobin S (HbS) percentage should be measured in all SCD patients with acute priapism. Exchange blood transfusion has also been proposed, with the aim of increasing tissue delivery of oxygen [1398]. The transfused blood should be sickle cell haemoglobin negative and Rh and Kell antigen matched [1399]; however, the evidence is inconclusive as to whether exchange transfusion itself helps to resolve priapism. A systematic review reported that the mean time to detumescence was eleven days with exchange transfusions compared to eight days with conventional treatment. Moreover, there were nine cases of ASPEN syndrome (association of SCD, priapism, exchange transfusion and neurological events) as a consequence of blood transfusion [1400].

A series of ten patients with SCD-related priapism showed that it was safe to perform exchange transfusion [1398]; however, several reports suggest that exchange transfusion may result in serious neurological sequelae [1400]. Therefore, routine use of exchange transfusion is not recommended as a primary treatment intervention in this group unless there is a risk of SCD-related symptoms. However, in patients who failed medical management, transfusion may be required to enable general anaesthesia to be safely administered prior to definitive surgery [1401].

10.1.3.2 Surgical management- second-line treatments

Second-line intervention typically refers to surgical intervention in the form of penile shunt surgery and penile implant insertion for refractory or delayed ischaemic priapism, and should only be considered when other medical management options have failed. There is no evidence detailing the time frames before moving

on to surgery after first-line treatment, although a period of at least 1 hour of first-line treatment without detumescence can be considered prior to moving to surgical intervention.

A number of clinical indicators suggest failure of first-line treatment including continuing corporal rigidity, cavernosal acidosis, anoxia, severe glucopenia, absence of cavernosal artery inflow by penile colour duplex US, and elevated intracorporal pressure [1402].

10.1.3.2.1 Penile shunt surgery

Penile shunt surgery aims to produce an outflow for ischaemic blood from the corpus cavernosum into the corpus spongiosal tissues, thereby allowing restoration of normal circulation within these structures. Accordingly, a shunt creates an opening in the tunica albuginea, with either the glans, corpus spongiosum, or a vein for blood drainage (Table 50) [1336, 1369, 1403].

The type of shunt procedure is chosen according to the surgeon's preference and familiarity with the procedure. It is conventional practice for distal shunt procedures to be tried before considering proximal shunting.

It is important to assess the success of surgery by direct observation of penile rigidity or by repeated testing (e.g., cavernous blood gas testing) [1336, 1369, 1404, 1405]. The use of penile colour US may not give appropriate information because of the hyperaemic (reperfusion) period that follows decompression after the ischaemic state [1406].

The recovery rates of erectile function in men undergoing shunt surgery following prolonged episodes of priapism are low and are directly related to the duration of priapism, pre-operative erectile status and age [1404, 1405, 1407]. If ischaemic priapism resolves within 24 hours of onset, it has been reported that 78-100% of patients regain spontaneous functional erections (with or without PDE5Is use). In contrast, other studies have shown that priapism for more than 36-48 hours appears to result in both structural and functional effects on corporal smooth muscle, with poorer outcomes (ED > 90%) [1404]. In general, shunt procedures undertaken after this period (36-48 hours) may only serve to limit pain without any beneficial effects on erectile function and early penile prosthesis insertion can be considered [1342, 1409].

Procedures for shunting require incision through the tunica albuginea and expose collagen to coagulation factors in the penile blood and thus activate the blood-clotting cascade. Peri-operative anti-coagulation is advocated to facilitate resolution of the priapism. There was an 84% decrease in priapism recurrence in the shunt group that received peri-procedural anti-thrombotic treatment (325 mg acetylsalicylic acid pre-operatively, and 5000 IU intraoperative heparin, 81 mg acetylsalicylic acid and 75 mg clopidogrel post-operatively for 5 days) compared with the group that did not receive peri-procedural anti-thrombotic treatment after failed aspiration [1410].

Four categories of shunt procedures have been reported [1336, 1370, 1403, 1409]. The limited data available does not allow one procedure to be recommended over another. However, distal shunts are less invasive and associated with lower rates of post-operative ED and therefore are recommended as the first surgical intervention of choice (Appendix 6 Table 10.1).

- *Percutaneous distal (corpora-glanular) shunts*

Winter's procedure uses a Trucut biopsy needle to create a fistula between the glans penis and each corpus cavernosum [1336, 1348, 1370, 1406, 1411]. Post-operative sequelae are uncommon [1412]. Winter's shunt is easy to perform, but has been reported as the least successful operation to create a distal shunt [1405]. This is because the diameter of the Trucut needle is only 1.6 mm (14-18 g) and therefore cannot accommodate the increased blood flow from post-ischaemic hyperaemia, resulting in poor drainage, increased intracavernous pressure and consequent premature closure of the shunt [1406].

Ebbehoj's technique involves making multiple tunical incision windows between the glans and each tip of the corpus cavernosum by means of a size 11 blade scalpel passed several times percutaneously [1336, 1370, 1406, 1413, 1414].

T-Shunt involves performing a bilateral procedure using a scalpel with a size 10 blade inserted through the glans just lateral to the urethral meatus until it enters the tip of the corpus cavernosum. The blade is then rotated 90° away (to the lateral side) from the urethral meatus and withdrawn [1336, 1370, 1406, 1415] (LE: 3). If unsuccessful, the procedure is repeated on the opposite side. The T-shunt can be followed by a tunnelling procedure using a size 8/10 Hegar dilator inserted through the glans and into the corpus cavernosum, which

can also be performed using US guidance, mainly to avoid urethral injury [1415]. The entry sites in the glans are sutured following detumescence. Tunnelling with a 7 mm metal sound or 7/8 Hegar dilator is necessary in patients with priapism duration > 48 hours. Tunnelling is a potentially attractive procedure as it combines the features of distal and proximal shunts with proximal drainage of the corpus cavernosum and may ameliorate the profibrotic effect of sludged blood retained in the corpus cavernosum [1407, 1409, 1415].

- *Open distal (corpora-glanular) shunts*

Al-Ghorab's procedure consists of an open bilateral excision of circular cone segments of the distal tunica albuginea via the glans penis, along with subsequent glans closure by running suture with absorbable material. A transverse incision on the glans may compromise arterial blood flow because distal deep dorsal arteries run longitudinally in the glans [1336, 1370, 1406, 1416-1418].

Burnett's technique (Snake manoeuvre) is a modification of the Al-Ghorab corpora-glanular shunt. It involves retrograde insertion of a 7/8 Hegar dilator into the distal end of each corpus cavernosum through the original Al-Ghorab glandular 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 is closed as in the Al-Ghorab procedure [1336, 1370, 1406, 1419, 1420]. Reported complications include wound infection, penile skin necrosis and urethrocutaneous fistulae [1420].

- *Open proximal (corpora-spongiosal) shunts*

Quackles's technique uses a trans-scrotal or perineal approach; a proximal open shunt technique creates a communication between the corpus cavernosum and the corpus spongiosum. The most frequent complications include an unwanted urethro-cavernous fistula and urethral stricture or cavernositis [1336, 1370, 1403, 1421]. The risk of urethral injury is less with a perineal approach to the bulb of the corpus spongiosum. Proximal shunts are more invasive and ED rates are documented to be higher [1402].

- *Peno-scrotal decompression*

More recently a proximal decompression technique with the aim to spare the glans with high success rates has been described. The technique is based upon opening of the proximal corpus cavernosum combined with proximal and distal tunnelling using a suction tip [1422]. In a cohort of 25 patients, 12 had undergone previous corpora-glanular shunt surgery. Recurrence was observed in two of 25 patients with unilateral peno-scrotal decompression. In the 15 patients who had follow-up data, 40% had ED. Whilst, representing a promising technique, PSD in cases of refractory priapism may further delay penile prosthesis insertion with detrimental effects on surgical outcomes including penile shortening and prosthetic infection.

- *Vein anastomoses/shunts*

Grayhack's procedure 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 [1336, 1370, 1423-1425].

10.1.3.2.2 Immediate penile prosthesis implantation

The studies pertaining to penile implantation surgery are principally retrospective non-randomised case series (Appendix 9 online supplementary evidence). All of the studies described priapism resolution rate, sexual function and surgical adverse events although the follow-up period was variable [1333].

Refractory, therapy-resistant, acute ischaemic priapism or episodes lasting more than 48 hours usually result in complete ED, and possibly significant penile deformity in the long-term. In these cases, immediate penile prosthesis implantation surgery is advocated [1426, 1427, 1429].

Gadolinium-enhanced penile MRI [1366] and cavernosal smooth muscle biopsy have been used to diagnose smooth muscle necrosis (which, if present, would suggest that shunting is likely to fail) and may help in decision-making and patient counselling in cases of refractory or delayed presentation (> 48 hours) that may be considered for immediate penile prosthesis insertion.

Early implantation of a penile prosthesis is associated with lower infection rates (6-7% vs. 19-30%), penile shortening (3% vs. 40%) and revision rates (9% vs. 27%) compared to late insertion. General satisfaction rate for early implantation is higher (96%) than for late implantation (60%) [1342] (Appendix 10 online supplementary evidence). Potential complications that could compromise immediate penile prosthesis implantation include distal erosion and infection [1426, 1428], along with a small rate of revision surgery [1426]. Early surgery also offers the opportunity to maintain penile length and girth and prevent penile curvature due to cavernosal

fibrosis. The prosthesis can be exchanged for an inflatable prosthesis at a later date, which may allow upsizing of the implant cylinders [1430].

The decision on which type of implant to insert is dependent on patient suitability, surgeons' experience, and availability and cost of the equipment. The immediate insertion of a malleable penile prosthesis is recommended to avoid the difficulty and complications of delayed prosthetic surgery in the presence of corporal fibrosis.

There are no randomised trials comparing the efficacy and complication rates of malleable and inflatable penile prostheses. Despite the higher infection rate in priapism patients compared to those with virgin prosthesis, in patients who are well-motivated and counselled prior to the procedure, immediate inflatable penile prosthesis implantation may be undertaken, although in most cases a semi-rigid implant is more suitable as it is easier to implant and reduces operative time and hence the risk of prosthetic infection. A further issue with immediate insertion of an inflatable penile prosthesis is that the patient must begin cycling the device immediately to avoid a fibrous capsule forming and contracting. Early cycling of an inflatable penile prosthesis prevents penile curvature and shortening [1342].

Currently, there are no clear indications for immediately implanting a penile prosthesis in men with acute ischaemic priapism, although this can be considered in men with delayed or refractory priapism [1369].

Relative indications include [1336]:

- Ischaemia that has been present for more than 48 hours.
- Failure of aspiration and sympathomimetic intracavernous injections in delayed priapism (> 48 hours).
- Magnetic resonance imaging or corporal biopsy evidence of corporal smooth muscle necrosis [1336, 1426].
- Failure of a shunting procedure; although, in delayed cases (> 48 hours), implantation might be considered ahead of shunt surgery.
- Refractory priapism in patients who have undergone shunting procedures.

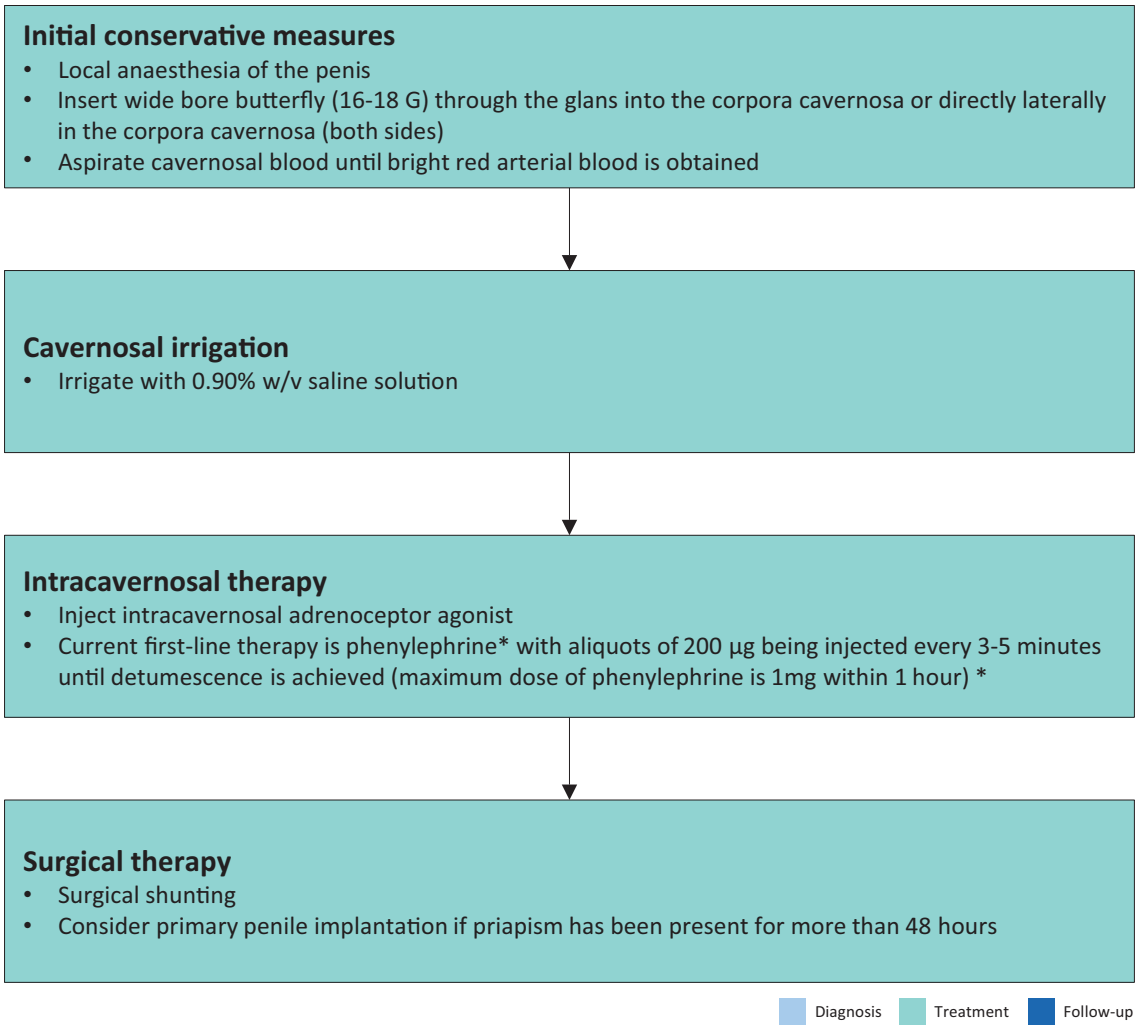
The optimal time for implantation is within the first three weeks from the priapism episode [1342, 1402, 1431]. If shunt surgery has been performed, penile prosthesis implantation can be further delayed in order to allow reduction of oedema, wound healing and risk of prosthetic infection. A vacuum device to avoid fibrosis and penile shortening may be used during this waiting period [1432].

10.1.3.2.3 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 [1403, 1426, 1433, 1434]. Erectile dysfunction is also often observed [1336, 1435]. Unfortunately, these outcomes can still occur despite apparently successful first or second-line treatment in detumescence of the penis.

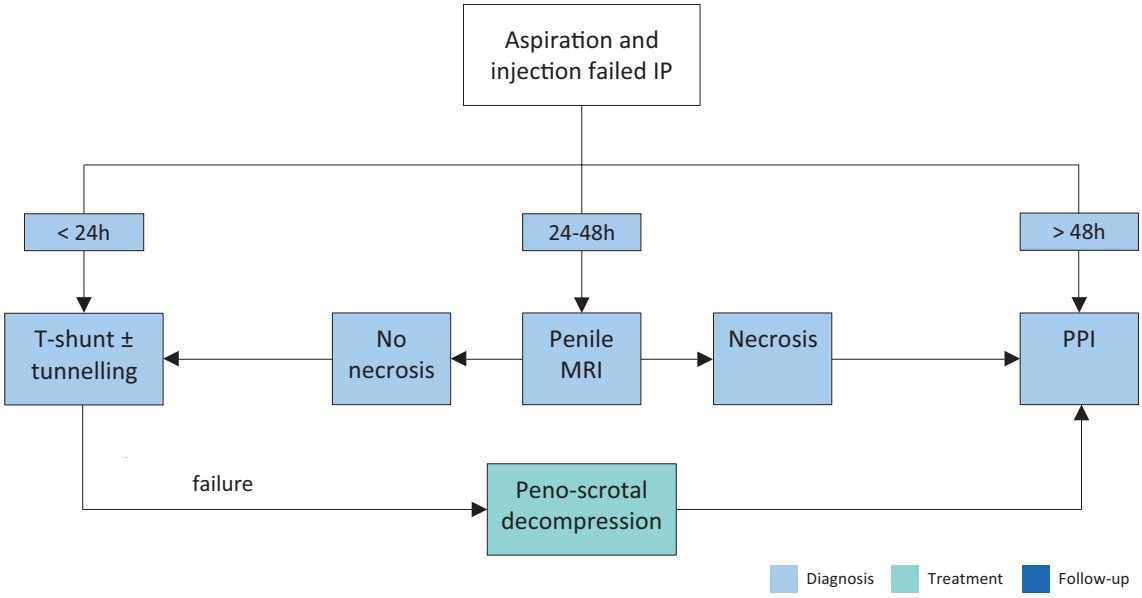
Penile prosthesis implantation is occasionally indicated in SCD patients with severe ED because other therapeutic options, such as PDE5Is and intracavernous injections are avoided as they may provoke a further priapism event [1336, 1369]. In severe corporal fibrosis, narrow-based prosthetic devices are preferable because they are easier to insert and need less dilatation [1426]. After severe priapism that has resulted in penile destruction with complicated deformities or even loss of penile tissue, it may be necessary to make changes to the surgical technique. Multiple corporotomies, corporal excavation, optical corporotomy-Shaeer technique, dilatation with Carrion-Rosello cavernotome, Uramix or Mooreville cavernotome, excision of scar tissue, and use of small-diameter prosthesis, or penile reconstruction using grafts can be utilised, if concomitant prosthesis implantation is considered [1408, 1436].

Figure 13: Management work-up of ischaemic priapism



(*) 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. Monitoring of pulse and blood pressure is advisable in all patients during administration and for one hour afterwards. Its use is contraindicated in men with a history of cerebro-vascular disease and significant hypertension.

Figure 14: Surgical management of priapism



MRI = Magnetic resonance imaging; PPI = penile prosthesis implantation; IP = ischaemic priapism.

10.1.4 Summary of evidence and recommendations for treatment of ischaemic priapism

Summary of evidence	LE
Ischaemic priapism is a medical emergency and immediate intervention is mandatory.	2b
Erectile function preservation is directly related to the duration of ischaemic priapism, age and pre-operative erectile status.	2b
Medical treatment is variably effective in case of priapism lasting less than 48 hours.	2b
Aspiration ± irrigation with 0.9% results in over 80% success rate when combined with intracavernous injection of sympathomimetic drugs.	2b
Phenylephrine is the recommended drug due to its favourable safety profile in the cardiovascular system compared to other drugs. Phenylephrine is usually diluted in normal saline with a concentration of 100-500 µg/mL and given in 200 µg doses every three to five minutes directly into the corpus cavernosum. Maximum dosage is 1 mg within one hour. Patient monitoring is highly recommended.	2b
Oral terbutaline has a success rate in up to 60% of cases when priapism is associated with intracavernous injection of erectogenic agents.	1b
Exchange transfusion in patients with priapism associated with SCD may result in serious neurological sequelae.	2b
Shunt procedures are effective to resolve priapism and provide pain relief. No clear recommendation of the superiority of one type of shunt over another can be given. Distal shunts are less invasive and associated with lower rate of erectile dysfunction.	2b
Peri- and post-operative anticoagulant prophylaxis (325 mg acetylsalicylic acid pre-operatively, 5,000 IU heparin intra-operatively and 81 mg acetylsalicylic acid and 75 mg clopidogrel five days post-operatively) may prevent priapism recurrence.	3
Erectile dysfunction is almost inevitable in prolonged cases or ischaemic priapism. Early implantation of penile prosthesis is associated with lower infection rates and complications compared to late implantation.	2b

Recommendations	Strength rating
Start management of ischaemic priapism as early as possible (within four to six hours) and follow a stepwise approach.	Strong
Decompress the corpus cavernosum by penile aspiration and washout until fresh red blood is obtained as first treatment step.	Strong

Replace blood aspiration with intracavernous injection of a sympathomimetic drug as the first step in priapism secondary to intracavernous injections of vasoactive agents.	Strong
Perform intracavernous injection of a sympathomimetic drug in priapism that persists despite aspiration.	Strong
Repeat aspiration and intracavernous injection of a sympathomimetic drug in cases that persist despite prior aspiration and intracavernous injection of a sympathomimetic drug, before considering surgical intervention.	Strong
Treat ischaemic priapism associated with sickle cell disease in the same fashion as idiopathic ischaemic priapism. Do not use exchange transfusion as a primary treatment. Provide other supportive measures (intravenous hydration, oxygen administration with alkalisation with bicarbonate, blood exchange transfusions), but do not delay initial treatment to the penis.	Strong
Proceed to surgical treatment only when blood aspiration and intracavernous injection of sympathomimetic drugs have failed.	Strong
Perform distal shunt surgical procedures first and combine them with tunnelling if necessary.	Weak
Use proximal procedures in cases of distal shunt failure (< 48 hours) or in patients who do not wish to proceed with immediate penile implant insertion.	Weak
Discuss implantation of a penile prosthesis in cases of delayed presentation (> 48 hours) and in cases refractory to injection therapy and distal shunting.	Weak
Delay implantation of a penile prosthesis if a shunt has been performed, to minimise the risk of infection and erosion of the implant.	Strong
Decide on which type of implant to insert based on: • patient suitability; • surgeons' experience; and • availability and cost of equipment. If a malleable penile prosthesis is implanted it can be exchanged later for an inflatable penile implant.	Strong

10.2 Priapism in Special Situations

*10.2.1 **Stuttering (recurrent or intermittent) priapism***

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-limiting with intervening periods of detumescence [1395, 1437]. These are analogous to repeated episodes of ischaemic priapism. In stuttering priapism the duration of the erections is generally shorter than in ischaemic priapism [1370]. The frequency and/or duration of these episodes are variable and a single episode can sometimes progress into prolonged ischaemic priapism.

Robust epidemiological studies of stuttering priapism are lacking [1438, 1439]. However, recurrent priapism episodes are common in men with SCD (42-64%) [1440, 1441] while in adolescents and young men the incidence of priapism is 35%, of whom 72% have a history of stuttering priapism [1438].

The aetiology of stuttering priapism is similar to that of ischaemic priapism. Whilst SCD is the most common cause, idiopathic cases and cases due to a neurological disorder have been reported. Men who have acute ischaemic priapism, especially which has been prolonged (for more than four hours) are at risk of developing stuttering priapism [1435].

Several studies have proposed alternative mechanisms for stuttering priapism including inflammation, cellular adhesion, NO metabolism, vascular reactivity and coagulation [1336, 1352, 1395, 1437, 1442-1445]. Although debated, androgens have also been observed to have an association with priapism [1446]. Therefore, one of the options for the treatment of stuttering priapism is to reduce serum testosterone levels to hypogonadal levels, which then suppresses androgen-associated mechanisms believed to be involved in triggering recurrent priapism.

10.2.1.1 Diagnostic evaluation

History, physical examination, laboratory testing and penile imaging follow the same principals as ischaemic priapism. In stuttering priapism there is a history of recurrent episodes of prolonged erections. These episodes can occur from several daily to isolated incidents every few months, continuously or followed by incident-free periods, of unknown duration, even months and years [1447]. The onset of the priapic episodes usually occurs

during sleep and detumescence does not occur upon waking. These episodes can be painful and may be the reason that the patient first seeks medical attention. 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 megalo-phallus.

Recommendations for the diagnosis of stuttering priapism are the same as those described in section 10.1.2.5

10.2.1.2 Disease management

The primary goal in the management of patients with stuttering priapism is the prevention of further episodes and limiting the chances of developing a prolonged ischaemic priapism that is refractory to conventional treatment options. In most cases, stuttering priapism can be managed by pharmacological treatment. The management of each acute episode is similar to that for ischaemic priapism; aspiration/irrigation in combination with intracavernous injections of α-adrenergic agonists.

10.2.1.2.1 α-Adrenergic agonists

Studies of oral α-adrenergic agonists have suggested some prophylactic benefit for daily treatment with these agents [1448]. Adverse effects include tachycardia and palpitations. Pseudoephedrine is widely used as an oral decongestant and can be a first-line treatment option for stuttering priapism [1390]. However, its effect on corporal smooth muscle is not fully understood. Etilephrine has been used successfully to prevent stuttering priapism caused by SCD. It is usually taken orally at doses of 5-10 mg daily, with response rates of up to 72% [1449-1451]. In a placebo-controlled RCT comparing medical prophylaxis with etilephrine and ephedrine, there was no difference in efficacy between the two drugs [1451].

10.2.1.2.2 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 [1351, 1395, 1452]. This can be achieved by GnRH agonists or antagonists, antiandrogens or oestrogens [1453, 1454]. Potential adverse effects may include hot flushes, gynaecomastia, ED, loss of libido, and asthenia. All approaches have a similar efficacy profile while the potential cardiovascular toxicity of oestrogens limits their clinical use. Alternative endocrine approaches that have been used with some success include 5-α-reductase inhibitors [1455, 1456] and ketoconazole; an anti-fungal agent that reduces adrenal and testicular androgen production [1452, 1457].

The duration of hormonal treatment for effective suppression of recurrent priapism is problematic. It is not possible to draw any conclusions on the dose, duration of treatment and the efficacy. Caution is strongly advised when prescribing hormonal treatments to pre-pubertal boys and adolescents, and specialist advice from paediatric endocrinologists should be sought. Likewise, hormonal agents have a contraceptive effect and interfere with normal sexual maturation and spermatogenesis and affect fertility. Therefore, men who are trying with their partner to conceive should be comprehensively counselled before using hormonal treatment. Moreover, sperm cryopreservation may be considered to mitigate any potential effects of anti-androgen therapy on fertility.

10.2.1.2.3 Digoxin

Digoxin is a cardiac glycoside and positive inotrope that is used to treat congestive heart failure. Digoxin regulates smooth muscle tone through several different pathways leading to penile detumescence [1351, 1395, 1458]. The use of maintenance digoxin doses (0.25-0.5 mg/daily) in idiopathic stuttering priapism reduces the number of hospital visits and improves QoL [1395]. In a small, clinical, double-blind, placebo-controlled study, digoxin decreased sexual desire and excitement with a concomitant reduction in penile rigidity, regardless of any significant change in plasma levels of testosterone, oestrogens and LH [1458]. Adverse effects include decreased libido, anorexia, nausea, vomiting, confusion, blurred vision, headache, gynaecomastia, rash and arrhythmia.

10.2.1.2.4 Terbutaline

Terbutaline has been used to prevent stuttering priapism with detumescence rates of 36% in patients with alprostadil-induced priapism [1390]. The only RCT (n = 68) in patients with pharmacologically-induced priapism, demonstrated detumescence in 42% of the terbutaline-treated group compared to only 15% in the placebo-treated group [1391]. Adverse effects include nervousness, shakiness, drowsiness, palpitations, headache, dizziness, hot flushes, nausea and weakness.

10.2.1.2.5 Gabapentin

Gabapentin has anticonvulsant, antinociceptive and anxiolytic properties and is widely used as an analgesic and anti-epileptic agent. Its proposed mechanism of action is to inhibit voltage-gated calcium channels, which attenuates synaptic transmission [1452], and reduces testosterone and FSH levels [1459]. It is given at a dose of 400 mg, four times daily, up to 2,400 mg daily, until complete penile detumescence occurs, with subsequent maintenance administration of 300 mg/daily [1460]. Adverse effects include anorgasmia and impaired erectile function.

10.2.1.2.6 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 [1351]. Oral baclofen has little efficacy and it is not usually used in stuttering priapism but intrathecal administration is more effective [1395, 1461-1463]. Adverse effects include drowsiness, confusion, dizziness, weakness, fatigue, headache, hypotension and nausea.

10.2.1.2.7 Hydroxyurea

Hydroxyurea blocks the synthesis of deoxyribonucleic acid (DNA) by inhibiting ribonucleotide reductase, which has the effect of arresting cells in the S-phase [1452, 1464]. Hydroxyurea is an established treatment for ameliorating SCD and improving life expectancy [1394, 1465]. For patients with recurrent priapism, there is limited evidence to suggest a prophylactic role of hydroxyurea [1452, 1464, 1466]. Adverse effects include oligo-zoospermia and leg ulcers.

10.2.1.2.8 Phosphodiesterase type 5 inhibitors

Low doses of PDE5Is have a paradoxical effect in alleviating and preventing stuttering priapism; mainly in patients with idiopathic and SCD-associated priapism [1351, 1395, 1443, 1467-1471]. 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.

10.2.1.2.9 Intracavernosal injections

Some patients with stuttering priapism, who have started on systemic treatment to prevent recurrence of unwanted erections, may not see therapeutic benefits immediately and temporarily require intracavernous self-injections at home with sympathomimetic agents [1351, 1395]. The most commonly used drugs are phenylephrine and etilephrine [1336, 1370, 1439, 1450].

Tissue plasminogen activator (TPA) is a secreted serine protease that converts the pro-enzyme plasminogen to plasmin, which acts as a fibrinolytic enzyme. Limited clinical data have suggested that a single intracavernous injection of TPA can successfully treat patients with recalcitrant priapism [1452, 1472]. Mild bleeding is the most commonly observed adverse effect.

10.2.1.2.10 Penile prosthesis

Patients with medically refractory stuttering priapism require frequent visits to the emergency department and are always at risk of a major ischaemic episode, which can be mitigated with insertion of a penile prosthesis [1408, 1429, 1473]. Nevertheless, penile prosthesis for preventing stuttering priapism should not be offered before medical treatment and a penile prosthesis should be performed only in carefully selected patients as a last resort [1408]. In patients with permanent ED due to stuttering priapism, medical treatments for ED should be used cautiously because of the risk of inducing an ischaemic episode and a penile prosthesis can be considered [1408, 1474].

10.2.1.3 Summary of evidence and recommendations for treatment of stuttering priapism

Summary of evidence	LE
The primary goal in the management of patients with stuttering priapism is prevention of future episodes, which can generally be achieved pharmacologically.	2b
Hormonal therapy with GnRH agonists or antagonists or antiandrogens is able to reduce the risk of recurrent priapism episodes although it is associated with adverse events (hot flushes, gynaecomastia, ED, loss of libido, asthenia and infertility)	3
Phosphodiesterase type 5 inhibitors have a paradoxical effect in alleviating and preventing stuttering priapism, mainly in patients with idiopathic and sickle cell disease-associated priapism.	3
The evidence with other systemic drugs (digoxin, α-adrenergic agonists, baclofen, gabapentin and terbutaline, hydroxyurea) is limited.	3

Recommendations	Strength rating
Manage each acute episode according to the treatment recommendations for ischaemic priapism (section 10.1.4).	Strong
Use hormonal therapies (mainly gonadotropin-receptor hormone agonists or antagonists) and/or anti-androgens for the prevention of future episodes in patients with frequent relapses. Do not use them before sexual maturation is reached.	Weak
Initiate treatment with phosphodiesterase type 5 inhibitors only when the penis is in its flaccid state.	Weak
Use digoxin, α-adrenergic agonists, baclofen, gabapentin or terbutaline only in patients with frequent and uncontrolled relapses.	Weak
Use intracavernous self-injections of sympathomimetic drugs at home for treatment of acute episodes on an interim basis until ischaemic priapism has been alleviated.	Weak

10.2.1.4 Follow-up

Follow-up for stuttering priapism includes history and clinical examination to assess the efficacy of treatment in preventing or alleviating erectile events as well as assessing erectile function and penile fibrosis.

*10.2.2 **Priapism in children***

The classification of priapism in children is similar to that in adults. In addition to ischaemic, stuttering and non-ischaemic priapism, a fourth type, neonatal priapism is also described [1336]. Priapism in children is considered rare as no data on its prevalence exist. Sickle cell disease is the major cause of priapism in children, followed by leukaemia (10%), trauma (10%), idiopathic causes (19%) and drugs (5%) [1475]. One study showed that 25% of children experienced SCD-related priapism in a pre-pubertal period [1476]. Another study revealed that 90% of men with SCD had their first priapism episode before age 20 years [1441]. Priapism in children should be evaluated and treated in a timely manner, as untreated ischaemic priapism may lead to ED and psychosexual disorders in adulthood [1477]. A multi-disciplinary team approach should be utilised with specialist input from haematologists and paediatric endocrinologists.

10.3 Non-ischaemic (high-flow or arterial) priapism

Non-ischaemic priapism is a persistent erection caused by unregulated cavernous arterial inflow [1336]. According to aetiology, non-ischaemic priapism can be categorised into four types: traumatic, neurogenic, iatrogenic and idiopathic in origin.

*10.3.1 **Epidemiology/aetiology/pathophysiology***

Epidemiological data on non-ischaemic priapism are almost exclusively derived from small case series [1336, 1364, 1478-1480]. Non-ischaemic priapism is significantly less common than the ischaemic type, comprising only 5% of all priapism cases [1336]. The most frequent cause of non-ischaemic priapism is blunt perineal or penile trauma [1481]. The injury results in a laceration in the cavernosal artery or branches, leading to a fistula between the artery and the lacunar spaces of the sinusoidal space [1480]. The resultant increased blood flow results in a persistent and prolonged erection [1482].

There is often a delay between the trauma and the development of the priapism that may be up to two to three weeks [1483]. This is 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 up". The priapism typically occurs after a nocturnal erection or an erection related to sexual activity, resulting in the sudden increase of blood flow and pressure in the cavernous arteries [1484]. The patient typically reports an erection that is not fully rigid and is not associated with pain because the venous drainage is not compromised and the penile tissue does not become ischaemic [1485].

Non-ischaemic priapism can occur after acute spinal cord injury, presumably due to loss of sympathetic input, leading to predominant parasympathetic input and increased arterial flow [1486]. It has also been reported to occur following internal urethrotomy [1487], Nesbit procedure [1488], circumcision [1489], transrectal prostate biopsy [1490], and brachytherapy for prostate cancer [1491]. Some cases have also been described following shunting procedures performed for ischaemic priapism due to a lacerated cavernosal artery (conversion of low-flow to high-flow priapism) [1492-1494]. Although SCD is usually associated with ischaemic priapism, occasional cases of high-flow priapism have been reported; however, the pathophysiological mechanism remains unclear [1495]. Finally, metastatic malignancy to the penis can also rarely cause non-ischaemic priapism [1496, 1497].

*10.3.2 **Diagnostic evaluation***

10.3.2.1 History

A comprehensive history is mandatory in non-ischaemic priapism diagnosis and follows the same principles as described in section 10.1.2.1. Arterial priapism should be suspected when the patient reports a history of pelvic, perineal, or genital trauma; no penile pain (discomfort is possible); and a persistent, not fully rigid erection. The corpus cavernosum can become fully rigid with sexual stimulation, so sexual intercourse is usually not compromised. The onset of post-traumatic non-ischaemic priapism can be delayed by several hours to weeks following the initial injury [1336].

10.3.2.2 Physical examination

In non-ischaemic priapism, the corpora are tumescent but not fully rigid. Abdominal, penile and perineal examination may reveal evidence of trauma [1336]. Neurological examination is indicated if a neurogenic aetiology is suspected.

10.3.2.3 Laboratory testing

Laboratory testing should include a blood count with white blood cell differential and a coagulation profile to assess for anaemia and other haematological abnormalities. Blood aspiration from the corpus cavernosum shows bright red arterial blood in arterial priapism, while blood is dark in ischaemic priapism. Blood gas analysis is essential to differentiate between non-ischaemic and ischaemic priapism. Blood gas values in high-flow priapism show normal arterial blood [1336] (Table 34).

10.3.2.4 Penile imaging

Colour duplex US of the penis and perineum is recommended and can differentiate non-ischaemic from ischaemic priapism [1362-1364]. Ultrasound must be performed without intracavernosal vasoactive drug injection [1498]. In non-ischaemic priapism, US helps to localise the fistula site and appears as a characteristic colour blush and turbulent high-velocity flow on Doppler analysis [1499]. Patients with non-ischaemic priapism have normal to high blood velocities in the cavernous arteries [1365, 1500].

Selective pudendal arteriography can reveal a characteristic blush at the site of injury in arterial priapism [1501, 1502]. However, due to its invasiveness, it should be reserved for the management of non-ischaemic priapism when embolisation is being considered [1336, 1359].

The role of MRI in the diagnostic evaluation of priapism is controversial. Its role in non-ischaemic priapism is limited because the small penile vessels and fistulae cannot be easily demonstrated [1503].

10.3.2.5 Summary of evidence and recommendations for the diagnosis of non-ischaemic priapism

Summary of evidence	LE
Non-ischemic priapism is less common than ischemic and is usually associated with blunt perineal or penile trauma leading to the development of intracavernosal fistula	2b
Medical history and blood gas analysis are able to differentiate between ischemic and non-ischemic priapism	2b
Blood aspiration from the corpora in case of non-ischemic priapism reveal bright red arterial blood with normal arterial gas values	2b
Penile duplex US is able to identify intracavernosal fistula responsible for non-ischemic priapism	2b

Recommendations	Strength rating
Take a comprehensive history to establish the diagnosis, which can help to determine the priapism subtype.	Strong
Include a physical examination of the genitalia, perineum and abdomen in the diagnostic evaluation.	Strong
Include a neurological examination if neurogenic non-ischaemic priapism is suspected.	Strong
Include complete blood count, white blood cell differential, and coagulation profile for laboratory testing.	Strong
Analyse the blood gas parameters from blood aspirated from the penis to differentiate between ischaemic and non-ischaemic priapism.	Strong
Perform colour duplex ultrasound of the penis and perineum to differentiate between ischaemic and non-ischaemic priapism.	Strong
Perform selected pudendal arteriography when embolisation is planned for non-ischaemic priapism.	Strong

10.3.3 ***Disease management***

Although the conventional belief is that the management of non-ischaemic priapism is not an emergency because the corpus cavernosum does not contain ischaemic blood; however, recent data indicate that the duration of non-ischaemic priapism can also impact EF. In a case series consisting of six patients with high-flow priapism after median follow-up of 4.5 (2-12) weeks, all patients reported development of ED or distal penile flaccidity [1430]. The goal of treatment is closure of the fistula. Non-ischaemic priapism can be managed conservatively or by direct perineal compression. Failure of conservative treatment requires selective arterial embolisation [1504]. The optimal time interval between conservative treatment and arterial embolisation is under debate. Definitive management can be performed at the discretion of the treating physician and should be discussed with the patient so that they can understand the risks of treatment [1336, 1359].

10.3.3.1 Conservative management

Conservative management may include applying ice to the perineum or perineal compression, which is typically US-guided. The fistula occasionally closes spontaneously. Even in cases where the fistula remains patent, intercourse is still possible [1364, 1479, 1505, 1506]. Androgen deprivation therapy (e.g., leuprolide injections, bicalutamide and ketoconazole) has been reported in case series to enable closure of the fistula reducing spontaneous and sleep-related erections [1507]. However, sexual dysfunction due to these treatments must be considered. Patients may develop ED or distal penile flaccidity while undergoing conservative treatment [1430].

Blood aspiration is not helpful for the treatment of arterial priapism and the use of α-adrenergic antagonists is not recommended because of potential severe adverse effects (e.g., transfer of the drug into the systemic circulation).

10.3.3.2 Selective arterial embolisation

Selective arterial embolisation can be performed using temporary substances, such as autologous blood clot [1508-1510] and gel foam [1509, 1511], or permanent substances such as microcoils [1509, 1511-1513], ethylene-vinyl alcohol copolymer (PVA), and N-butyl-cyanoacrylate (NBCA) [1514]. It is assumed that temporary embolisation provides a decreased risk of ED, with the disadvantage of higher failure/recurrence rates, as a consequence of artery embolisation using temporary materials. However, there is insufficient evidence to

support this hypothesis. Success rates ranging between 61.7 and 83.3%, and ED rates from 0-33.3% after the first arterial embolization have been reported, suggesting that failure/recurrence may not be significantly higher with temporary embolisation materials, and preservation of erectile function may not be that different between the two modalities either [1484]. Other potential complications of arterial embolisation include penile gangrene, gluteal ischaemia, cavernositis, and perineal abscess [1336, 1515]. Repeated embolisation is a reasonable option for treating non-ischaemic priapism, both in terms of efficacy and safety [1484].

10.3.3.3 Surgical management

Surgical ligation of the fistula is possible through a transcorporeal or inguinoscrotal approach, using intra-operative Doppler US. Surgery is technically challenging and associated with significant risks, particularly of ED [1516]. Surgery is rarely performed and should only be considered when there are contraindications for selective embolisation, if embolisation is unavailable, or repeated embolisations have failed. If the patient desires more definitive treatment and is not sexually active or has pre-existing ED, surgical intervention can be an appropriate option [1484]. Erectile dysfunction rates ranging from 0-50% have been reported following treatment for non-ischaemic priapism, with surgical ligation having the highest reported rates [1484]. Patients can require penile prosthesis implantation for ED in the long-term [1408].

10.3.3.4 Summary of evidence and recommendations for the treatment of non-ischaemic priapism

Summary of evidence	**LE**
Non-ischaemic priapism can cause erectile dysfunction over time and early definitive management should be undertaken.	3
Conservative management applying ice to the perineum or site-specific perineal compression is an option in all cases. The use of androgen deprivation therapy may enable closure of the fistula reducing spontaneous and sleep-related erections.	3
Selective 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 and success rate.	3
Repeated embolisation is a reasonable option for the treatment of non-ischaemic priapism.	2b
Selective surgical ligation of the fistula is associated with high risk of erectile dysfunction.	3

Recommendations	**Strength rating**
Perform definitive management for non-ischaemic priapism at the discretion of the treating physician as it is not a medical emergency.	Weak
Manage non-ischaemic priapism conservatively with the use of site-specific perineal compression as the first step. Consider androgen deprivation therapy only in adults.	Weak
Perform selective arterial embolisation when conservative management has failed.	Strong
Perform the first selective arterial embolisation using temporary material.	Weak
Repeat selective arterial embolisation with temporary or permanent material for recurrent non-ischaemic priapism following selective arterial embolisation.	Weak
Reserve selective surgical ligation of a fistula as a final treatment option when repeated arterial embolisations have failed.	Weak

10.3.3.5 High-flow priapism in children

Non-ischaemic priapism is a rare condition, especially in children. The embarrassment that children may have in speaking about it to their parents can lead to misdiagnosis and underestimating the prevalence of this condition [1517]. The aetiology, clinical presentation, diagnostic and therapeutic principles are comparable with those of arterial priapism in adults. However, some differentiating features should be noted.

Idiopathic non-ischaemic priapism can be found in a significant percentage of children [1518]. Perineal compression with the thumb may be a useful manoeuvre to distinguish ischaemic and non-ischaemic priapism, particularly in children, where it may result in immediate detumescence, followed by the return of the erection with the removal of compression [1484]. Conservative management using ice applied to the perineum or site-specific perineal compression may be successful, particularly in children [1519, 1520]. Although reportedly successful, embolisation in children is technically challenging and requires treatment within a specialist paediatric vascular radiology department [1374, 1521].

10.3.3.6 Follow-up

During conservative management of non-ischaemic priapism, physical examination and colour duplex US can be useful tools to assess treatment efficacy. Close follow-up using colour duplex US and MRI can help detect distal penile fibrosis and be beneficial in clinical decision-making to intervene with embolisation earlier [1430]. Follow-up after selective arterial embolisation should include clinical examination, colour duplex US, and erectile function assessment. If in doubt, repeat arteriography is required. The goals are to determine if the treatment was successful, identify signs of recurrence, and verify any anatomical and functional sequelae [1498].

11. MALE INFERTILITY

11.1 Definition and classification

Infertility is defined by the inability of a sexually active, non-contraceptive couple to achieve spontaneous pregnancy within twelve months [1522]. Primary infertility refers to couples that have never had a child and cannot achieve pregnancy after at least 12 consecutive months having sex without using birth control methods. Secondary infertility refers to infertile couples who have been able to achieve pregnancy at least once before (with the same or different sexual partner).

In 30-40% of cases, no male-associated factor is found to explain the underlying impairment of sperm parameters and historically was referred to as 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, although semen analysis may reveal pathological findings (see Section 11.3.2). It is now believed that idiopathic male infertility may be associated with several previously unidentified pathological factors, which include but are not limited to endocrine disruption as a result of environmental pollution, generation of reactive oxygen species (ROS)/sperm DNA damage, or genetic and epigenetic abnormalities [1523]. Unexplained male infertility is defined as infertility of unknown origin with normal sperm parameters and partner evaluation. Between 20 and 30% of couples will have unexplained infertility.

11.2 Epidemiology/aetiology/pathophysiology/risk factors

*11.2.1 **Introduction***

About 15% of couples do not achieve pregnancy within one year and seek medical treatment for infertility [1524]. One in eight couples encounter problems when attempting to conceive a first child and one in six when attempting to conceive a subsequent child [1525]. In 50% of involuntarily childless couples, a male-infertility-associated factor is found, usually together with abnormal semen parameters [1522]. For this reason, in all infertile couples the male should undergo medical evaluation by a urologist trained in male reproduction.

Male fertility can be impaired as a result of many different conditions (Table 36), thus including [1522]:

- congenital or acquired urogenital abnormalities;
- genetic abnormalities;
- varicocele;
- urogenital tract infections;
- increased scrotal temperature (e.g., as a consequence of varicocele);
- endocrine disturbances;
- immunological factors;
- iatrogenic factors (e.g., previous scrotal surgery);
- malignancy;
- gonadotoxic exposure (e.g., radiotherapy or chemotherapy);

Advanced paternal age has emerged as one of the main risk factors associated with the progressive increase in the prevalence of male factor infertility [1526-1533].

Advanced maternal age must be considered in the management of every infertile couple, and in the subsequent decisions throughout the diagnostic and therapeutic strategy of the male partner [1534, 1535]. This should include the age and ovarian reserve of the female partner, since these parameters might determine decision-making in terms of timing and therapeutic strategies (e.g., assisted reproductive technology [ART] vs. surgical intervention) [1526-1529]. Earlier evaluation is still a matter of debate in couples in with female partners older than 35 years who have not conceived for 6 months as ovarian reserve may fall [1536-1538].

Table 36 summarises the main male-infertility-associated factors.

Table 36: Male infertility causes and associated factors and percentage of distribution in 10,469 patients [1539]

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 auto-antibodies	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 syndrome (47, XXY)	2.6	13.7
XX male	0.1	0.6
Primary hypogonadism of unknown cause	2.3	0.8
Secondary (hypogonadotropic) hypogonadism	1.6	1.9
Kallmann syndrome	0.3	0.5
Idiopathic hypogonadotropic hypogonadism	0.4	0.4
Residual after pituitary surgery	< 0.1	0.3
Late-onset hypogonadism	2.2	-
Constitutional delay of puberty	1.4	-
Others	0.8	0.8
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 (congenital bilateral absence of vas deferens)	0.5	3.0
Others	0.8	1.9

11.2.2 Summary of evidence and recommendations on epidemiology and aetiology of male infertility

Summary of evidence	LE
Infertility affects 15% of couples of reproductive age.	3
A male factor infertility can be identified in about 50% of infertile couples.	2a
A pure male factor infertility can be identified in about 20% of infertile couples.	2a
Several risk factors such as genetic factors, urogenital abnormalities, endocrine disorders, malignant diseases and gonadotoxic treatments can cause male infertility.	2a

Recommendations	Strength rating
Perform infertility evaluation in couples who have not conceived after twelve months of regular, unprotected intercourse.	Strong
Investigate both partners simultaneously to categorise the cause of infertility.	Strong
Investigate all men belonging to couples seeking medical help for fertility problems.	Strong

11.3 Diagnostic work-up

Important treatment decisions are based on the results of semen analysis and most studies indicate semen parameters are a surrogate outcome for male fertility. However, a semen analysis *per se* cannot distinguish fertile from infertile men [1540].

The Guidelines panel concludes that a comprehensive andrological examination is always indicated in infertile couples, both if semen analysis shows abnormalities and in men with normal sperm parameters as compared with reference values [1541-1543].

Focused evaluation of male patients should include: a medical and reproductive history; physical examination; semen analysis – with strict adherence to World Health Organization (WHO) reference values for human semen characteristics [1544, 1545], and hormonal evaluation [1546]. Other investigations (e.g., genetic analysis and imaging) may be required depending on the clinical features and semen parameters.

*11.3.1 **Medical/reproductive history and physical examination***

11.3.1.1 Medical and reproductive history

Medical history should evaluate any risk factors and behavioural patterns that could affect male partner's fertility, such as lifestyle, family history (including, testicular cancer), comorbidities (including systemic diseases; e.g., hypertension, diabetes mellitus, obesity, MetS, testicular cancer, etc.), genito-urinary infections (including sexually transmitted infections), history of testicular surgery and exclude any potential known gonadotoxic medication or recreational drugs [1547].

Typical findings from the history of a patient with infertility include:

- cryptorchidism (uni- or bilateral);
- testicular torsion and trauma;
- genitourinary infections;
- exposure to environmental toxins;
- gonadotoxic medications (e.g., anabolic drugs, chemotherapeutic agents, etc.);
- exposure to radiation or cytotoxic agents.

11.3.1.2 Physical examination

A focused physical examination is compulsory in the evaluation of every infertile male, including presence of secondary sexual characteristics. The size, texture and consistency of the testes must be evaluated. In clinical practice, testicular volume is assessed by Prader's orchidometer [1548]; orchidometry may over-estimate testicular volume compared to US assessment [1549]. There are no uniform reference values in terms of Prader's orchidometer-derived testicular volume, due to differences in the populations studied (e.g., geographic area, nourishment, ethnicity and environmental factors) [1548-1550]. The mean Prader's orchidometer-derived testis volume reported in the European general population is 20.0 ± 5.0 mL [1548], whereas in infertile patients it is 18.0 ± 5.0 mL [1548, 1551-1553]. The presence of the vas deferens, fullness of epididymis and presence of a varicocele should be always determined. Likewise, palpable abnormalities of the testis, epididymis, and vas deferens should be evaluated. Other physical alterations, such as abnormalities of the penis (e.g., phimosis, short frenulum, fibrotic nodules, epispadias, hypospadias, etc.), abnormal body hair distribution and gynecomastia, should also be evaluated.

Typical findings from the physical examination of a patient with characteristics suggestive for testicular deficiency include:

- abnormal secondary sexual characteristics;
- abnormal testicular volume and/or consistency;
- testicular masses (potentially suggestive of cancer);
- absence of testes (uni-bilaterally);
- gynaecomastia;
- varicocele.

*11.3.2 **Semen analysis***

The 6th edition the WHO Manual for the Examination and Processing of Human Semen [1545] has been published on July 2021 and comprises of three sections: i) semen examination; ii) sperm preparation and cryopreservation; and, iii) quality assessment and quality control.

Procedures for semen examination are divided:

- Basic examinations, that should be performed by every laboratory, based on standardised procedures and evidence-based techniques.
- Extended analyses, which are performed by choice of the laboratory or by special request from the clinicians.
- Advanced examinations.

Basic examination summary [1544]:

- Assessment of sperm numbers: the laboratory should not stop assessing the number of sperm at low concentrations (2 million/mL), as suggested in the 5th edition, but report lower concentrations, noting that the errors associated with counting a small number of spermatozoa may be high. It is recognised that the total sperm numbers per ejaculate (sperm output) have more diagnostic value than sperm concentration; therefore, semen volume must be measured accurately.
- Assessment of sperm motility: the categorisation of sperm motility has reverted back to fast progressively motile, slow progressively motile, non-progressively motile and immotile (grade a, b, c or d) because presence (or absence) of rapid progressive spermatozoa is recognised to be clinically important.
- Assessment of sperm morphology: the 6th edition has recommended the Tygerberg strict criteria by sperm adapted Papanicolaou staining.
- Assessment of vitality should not be performed in all samples, only if more than 60% of spermatozoa are immotile.

Extended examinations

This chapter contains procedures to detect leukocytes and markers of genital tract inflammation, sperm antibodies, indices of multiple sperm defects, sequence of ejaculation, methods to detect sperm aneuploidy, semen biochemistry and sperm DNA fragmentation.

Reference ranges and reference limits

The lower fifth percentile of the distribution of semen analysis values from approximately 3500 men in 12 countries who have contributed to a natural conception within 12 months of trying does not represent a limit between fertile and infertile men. For a general prediction of live birth *in vivo* as well as *in vitro*, a multiparametric interpretation of the entire men's and partner's reproductive potential are needed. Reference values for semen parameters are represented in Table 37 [1541].

Moreover, more complex testing (e.g., sperm DNA fragmentation) than classic semen analysis may be required in everyday clinical practice, particularly in men belonging to couples with recurrent pregnancy loss from natural conception or ART and in men with unexplained male infertility. Although definitive conclusions cannot be drawn, given the heterogeneity of the studies, increased sperm DNA damage is associated with pregnancy failure [1523, 1554, 1555].

Table 37: Lower reference limits (5th centiles and their 95% CIs) for semen characteristics

Parameter	**2021 Lower reference limit (95% CI)**
Semen volume (mL)	1.4 (1.3-1.5)
Total sperm number (106/ejaculate)	39 (35-40)
Sperm concentration (106/mL)	16 (15-18)
Total motility (PR + NP, %)	42 (40-43)
Progressive motility (PR, %)	30 (29-31)
Vitality (live spermatozoa, %)	54 (50-56)
Sperm morphology (normal forms, %)	4 (3.9-4.0)

Other consensus threshold values	
pH	> 7.2
Peroxidase-positive leukocytes (10^6/mL)	< 1.0
Tests for antibodies on spermatozoa	
MAR test (motile spermatozoa with bound particles, %)	No evidence-based reference values. Each laboratory should define its normal reference ranges by testing a sufficiently large number of fertile men.
Immunobead test (motile spermatozoa with bound beads, %)	No evidence-based reference limits.
Accessory gland function	
Seminal zinc (µmol/ejaculate)	≥ 2.4
Seminal fructose (µmol/ejaculate)	≥ 13
Seminal neutral α-glucosidase (mU/ejaculate)	≥ 20

CIs = confidence intervals; MAR = mixed antiglobulin reaction; NP = non-progressive; PR = progressive (a+b motility).

** Distribution of data from the population is presented with one-sided intervals (extremes of the reference population data). The lower 5th percentile represents the level under which only results from 5% of the men in the reference population were found.*

If semen analysis is normal according to WHO criteria, a single test is sufficient. If the results are abnormal on at least two tests, further andrological investigation is indicated.

None of the individual sperm parameters (e.g., concentration, morphology and motility), are diagnostic *per se* of infertility. According to WHO reference criteria 5th edn., it is important to differentiate between the following [1556]:

- oligozoospermia: < 16 million sperm/mL;
- asthenozoospermia: < 32% progressive motile sperm;
- teratozoospermia: < 4% normal forms.

According to the WHO reference criteria 6th edn., this subdivision is not reported, although the EAU Guidelines panel considers this further segregation still clinically relevant in the everyday clinical practice.

Often, all three anomalies occur simultaneously, which is defined as oligo-astheno-terato-zoospermia (OAT) syndrome. As in azoospermia (namely, the complete absence of spermatozoa in semen), in severe cases of oligozoospermia (spermatozoa < 5 million/mL) [1557], there is an increased incidence of obstruction of the male genital tract and genetic abnormalities. In case of azoospermia, full andrological investigation should be warranted to classify obstructive azoospermia (OA) versus non-obstructive azoospermia (NOA). A recommended method to diagnose absolute azoospermia versus cryptozoospermia is semen centrifugation at 3,000 g for 15 minutes and a thorough microscopic examination by phase contrast optics at ×200 magnification of the pellet. All samples can be stained and re-examined microscopically [1558]. This is to ensure that small quantities of sperm are detected, which may be potentially used for intra-cytoplasmic sperm injection (ICSI); therefore removing the need for surgical intervention.

Advanced examinations

Obsolete tests such as the human oocyte and human zona pellucida binding and the hamster oocyte penetration tests have been completely removed. Research tests include assessment of ROS and oxidative stress, membrane ion channels, acrosome reaction and sperm chromatin structure and stability, computer-assisted sperm analysis (CASA).

Measurement of Oxidative Stress

Oxidative stress is considered to be central in male infertility by affecting sperm quality, function, as well as the integrity of sperm [1559]. Oxidative stress may lead to sperm DNA damage and poorer DNA integrity, which are associated with poor embryo development, miscarriage and infertility [1560, 1561]. Spermatozoa are vulnerable to oxidative stress and have limited capacity to repair damaged DNA. Oxidative stress is generally associated with poor lifestyle (e.g., smoking) and environmental exposure, and therefore antioxidant regimens and lifestyle interventions may reduce the risk of DNA fragmentation and improve sperm quality [1562]. However, these data have not been supported by RCTs. Although ROS can be measured by various assays (e.g., chemiluminescence),

no standardised testing methods for ROS are available and routine measurement of ROS testing should remain experimental until these tests are validated in RCTs [1563].

11.3.3 ***Measurement of sperm DNA Fragmentation Index (DFI)***

Sperm DNA fragmentation, or the accumulation of single- and double-strand DNA breaks occur in sperm, and an increase in the level of sperm DNA fragmentation has been shown to reduce the chances of natural conception [1564]. Although no studies have unequivocally and directly tested the impact of sperm DNA damage on the clinical management of infertile couples, sperm DNA damage is more common in infertile men and has been identified as a major contributor to male infertility, as well as poorer outcomes following ART [1565, 1566], including impaired embryo development [1565], miscarriage, recurrent pregnancy loss [1554, 1555, 1567], and birth defects [1565]. Sperm DNA damage can be increased by several factors including hormonal anomalies, varicocele, chronic infection and lifestyle factors (e.g., smoking) [1566].

Several assays have been described to measure sperm DNA damage. It has been suggested that current methods for assessing sperm DNA integrity still do not reliably predict treatment outcomes from ART and there is controversy whether to recommend them routinely for clinical use [1566, 1568, 1569]. Terminal deoxynucleotidyl transferase mediated deoxyuridine triphosphate nick end labelling (TUNEL) and the alkaline comet test (COMET) directly measure DNA damage. Conversely, sperm chromatin structure assay (SCSA) and sperm chromatic dispersion test (SCD) are indirect tools for DNA fragmentation assessment. The SCSA is still the most widely studied and one of the most commonly used techniques to detect sperm DNA damage [1570, 1571]. In SCSA, the number of cells with DNA damage is indicated by the DNA fragmentation index (DFI) [1572], whereas the proportion of immature sperm with defects in the histone-to-protamine transition is indicated by high DNA stainability [1573]. It is suggested that a threshold DFI of 25% as measured with SCSA, is associated with reduced pregnancy rates via natural conception or intra-uterine insemination (IUI) [1571]. Furthermore, DFI values > 50% on SCSA are associated with poorer outcomes from *in vitro* fertilisation (IVF). More recently, the mean COMET score and scores for proportions of sperm with high or low DNA damage have been shown to be of value in diagnosing male infertility and providing additional discriminatory information for the prediction of both IVF and ICSI live births [1566].

- *Testicular sperm in men with raised SDF in ejaculated sperm*

Testicular sperm is reported to have lower levels of SDF compared to ejaculated sperm [1574]. The use of testicular sperm for ICSI is associated with possibly improved outcomes compared with ejaculated sperm in men with high sperm DNA fragmentation [1574, 1575]. Men with unexplained infertility with raised DNA fragmentation may be considered for TESE after failure of ART, although they should be counselled that live-birth rates are under reported in the literature and patients must weigh up the risks of performing an invasive procedure in a potentially normozoospermic or unexplained condition. The advantages of the use of testicular sperm in men with cryptozoospermia have not yet been confirmed in large scale randomised studies [1576]. A recent meta-analysis has suggested that TESE-ICSI may improve the outcomes from ART but there is significant heterogeneity of data and the authors suggest that RCTs are needed to validate the use of TESE in men with raised SDF [1577].

In terms of a practical approach, urologists may offer the use of testicular sperm in patients with high SDF. However, patients should be counselled regarding the low levels of evidence for this (i.e., non-randomised studies). Furthermore, testicular sperm should only be used in this setting once the common causes of oxidative stress have been excluded, including varicoceles, modifications of dietary/lifestyle factors and treatment of accessory gland infections.

11.3.4 ***Hormonal determinations***

In men with testicular deficiency, hypergonadotropic hypogonadism (also called primary hypogonadism) is usually present, with high levels of FSH and LH and, with or without low levels of testosterone. Generally, the levels of FSH negatively correlate with the number of spermatogonia [1578]. When spermatogonia are absent or markedly diminished, FSH level is usually elevated; when the number of spermatogonia is normal, but maturation arrest exists at the spermatocyte or spermatid level, FSH level is usually within the normal range [1578]. However, for patients undergoing TESE, FSH levels do not accurately predict the presence of spermatogenesis, as men with maturation arrest on histology can have both normal FSH and testicular volume [1579, 1580]. Furthermore, men with NOA and high levels of FSH may still harbour focal areas of spermatogenesis at the time of TESE or microdissection TESE (mTESE) [1580, 1581]. Despite current findings need to be confirmed, growing data suggest that lower preoperative serum anti-Müllerian hormone (AMH) levels are associated with higher likelihood of positive sperm retrieval outcomes in men undergoing mTESE [1582, 1583].

11.3.5 ***Genetic testing***

All urologists working in andrology must have an understanding of the genetic abnormalities most commonly associated with infertility, so that they can provide correct advice to couples seeking fertility treatment. Current routine clinical practice in genetic testing is based on the screening of genomic DNA from peripheral blood samples. However, screening of chromosomal anomalies in spermatozoa (sperm aneuploidy) and preimplantation genetic testing (PGT) are also feasible and indicated in selected cases (e.g., recurrent miscarriage) [1584-1590].

11.3.5.1 Chromosomal abnormalities

Chromosomal 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% [1591]. 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 new-born male infants, of whom 131 (0.14%) had sex chromosomal abnormalities and 232 (0.25%) autosomal abnormalities [1591]. The frequency of chromosomal abnormalities increases as testicular deficiency becomes more severe. Patients with sperm count < 5 million/mL already show a 10-fold higher incidence (4%) of mainly autosomal structural abnormalities compared to the general population [1592, 1593]. Men with NOA are at highest risk, especially for sex chromosomal anomalies (e.g., Klinefelter syndrome) [1594, 1595].

Based on the frequencies of chromosomal aberrations in patients with different sperm concentration, karyotype analysis is currently indicated in men with azoospermia or oligozoospermia (spermatozoa < 10 million/mL) [1593]. Notwithstanding, the clinical value of spermatozoa < 10 million/mL remains a valid threshold until further studies, evaluating the cost-effectiveness, in which costs of adverse events due to chromosomal abnormalities (e.g., miscarriages and children with congenital anomalies) are performed [1596].

11.3.5.1.1 Sex chromosome abnormalities (Klinefelter syndrome and variants [47,XXY; 46,XY/47, XX mosaicism])

Klinefelter syndrome is the most common sex chromosomal abnormality [1597]. Adult men with Klinefelter syndrome usually have small firm testes along with features of primary hypogonadism. The phenotype is the final result of a combination between genetic, hormonal and age-related factors [12]. The phenotype varies from that of a normally virilised male to one with the stigmata of androgen deficiency. In most cases infertility and reduced testicular volume are the only clinical features that can be detected. Leydig cell function is also commonly impaired in men with Klinefelter syndrome and thus testosterone deficiency is more frequently observed than in the general population [1598], although rarely observed during the peri-pubertal period, which usually occurs in a normal manner [12, 1599]. Rarely, more pronounced signs and symptoms of hypogonadism can be present, along with congenital abnormalities including heart and renal problems [1600].

The presence of germ cells and sperm production are variable in men with Klinefelter syndrome and are more frequently observed in mosaicism, 46,XY/47,XXY. In patients with azoospermia, TESE or mTESE are therapeutic options as spermatozoa can be recovered in up to 50% of cases [1601, 1602]. Although the data are not unique [1602], there is growing evidence that TESE or mTESE yields higher sperm recovery rates when performed at a younger age [1594, 1603].

Since Klinefelter syndrome is associated with several general health problems, appropriate medical follow-up is therefore advised [13, 1604, 1605]. Testosterone therapy may be considered if testosterone levels are in the hypogonadal range when fertility issues have been addressed [15]. Moreover, men with Klinefelter syndrome are at higher risk of metabolic and cardiovascular diseases (CVD), including venous thromboembolism (VTE) and diabetes, particularly when starting testosterone therapy [1606]. In addition, a higher risk of haematological malignancies has been reported in men with Klinefelter syndrome [13].

Testicular sperm extraction in peri-pubertal or pre-pubertal boys with Klinefelter syndrome aiming at cryopreservation of testicular spermatogonial stem cells is still considered experimental and should only be performed within a research setting [1607]. The same applies to sperm retrieval in older boys who have not considered their fertility potential [1608].

11.3.5.1.2 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. When IVF/ICSI is carried out for men with translocations, PGD or amniocentesis should be performed [1609, 1610].

11.3.5.2 Cystic fibrosis gene mutations

Cystic fibrosis (CF) is an autosomal-recessive disorder [1611]. 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. Approximately 2,000 CFTR mutations have been identified and any CFTR alteration may lead to congenital bilateral absence of the vas deferens (CBAVD). However, only those with homozygous mutations exhibit CF disease [1612]. Congenital bilateral absence of the vas deferens is a rare reason of male factor infertility, which is found 1% of infertile men and in up to 6% of men with obstructive azoospermia [1613]. Clinical diagnosis of absent vasa is easy to miss and all men with azoospermia should be carefully examined to exclude CBAVD, particularly those semen volume < 1.0 mL and acidic pH < 7.0 [1614-1616]. In patients with CBAVD-only or CF, epididymal sperm aspiration (micro or percutaneous; MESA and PESA respectively), TESA, or TESE in combination with ICSI, can be used to achieve pregnancy. However, higher sperm quality, easier sperm retrieval and better ICSI outcomes are associated with CBAVD-only patients as compared with CF patients [1612].

The most frequently found mutations are F508, R117H and W1282X (according to their traditional definitions), but their frequency and the presence of other mutations largely depend on the ethnicity of the patient [1617, 1618]. Given the functional relevance of a DNA variant (the 5T allele) in a non-coding region of CFTR [1619], it is now considered a mild CFTR mutation rather than a polymorphism and it should be analysed in each CBAVD patient. 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 his partner for CF mutations. If the female partner is found to be a carrier of CFTR mutations, the couple must consider carefully whether to proceed with ICSI, 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% [1620].

11.3.5.2.1 Unilateral or bilateral absence/abnormality of the vas and renal anomalies

Congenital unilateral absence of the vas deferens (CUAVD) is usually associated with ipsilateral absence of the kidney and probably has a different genetic causation [1621]. Cystic fibrosis transmembrane conductance regulator gene mutation screening is indicated in men with unilateral absence of the vas deferens with normal kidneys. The prevalence of renal anomalies is rare for patients who have CBAVD and CFTR mutations [1622]. Abdominal US should be undertaken both in unilateral and bilateral absence of vas deferens without CFTR mutations. Findings may range from CUAVD with ipsilateral absence of the kidney, to bilateral vessel and renal abnormalities, such as pelvic kidney [1623].

11.3.5.3 Y microdeletions – partial and complete

Microdeletions on the Y-chromosome are termed AZFa, AZFb and AZFc deletions [1624]. 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 [1625]. In each AZF region, there are several spermatogenesis candidate genes [1626].

11.3.5.3.1 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 [1627].
- The highest frequency of Y-deletions is found in azoospermic men (8-12%), followed by oligozoospermic (3-7%) men [1628, 1629].
- Deletions are extremely rare with a sperm concentration > 5 million/mL (~0.7%) [1630].
- 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%) [1631].

- Complete deletion of the AZFa region is associated with severe testicular phenotype (Sertoli cell only syndrome [SCOS]), while complete deletions of the AZFb region is associated with spermatogenic arrest. Complete deletions that include the AZFa and AZFb regions are of poor prognostic significance for retrieving sperm with TESE. Therefore, TESE should not be attempted in these patients [1632, 1633].
- Deletions of the AZFc region causes a variable phenotype ranging from azoospermia to oligozoospermia.
- Testicular sperm can be found in 50-75% of men with AZFc microdeletions [1632-1634].
- Men with AZFc microdeletions who are oligo-azoospermic or in whom sperm is found at the time of TESE must be counselled that any male offspring will inherit the deletion.
- Classical (complete) AZF deletions do not confer a risk for cryptorchidism or testicular cancer [1630, 1635].

The specificity and genotype/phenotype correlation reported above means that Y-deletion analysis has both a diagnostic and prognostic value for testicular sperm retrieval [1635].

11.3.5.3.1.1 Testing for Y microdeletion

Historically, indications for AZF deletion screening are based on sperm count and include azoospermia and severe oligozoospermia (spermatozoa count < 5 million/mL). A meta-analysis assessing the prevalence of microdeletions on the Y chromosome in oligo-zoospermic men in 37 European and North American studies (n = 12,492 oligo-zoospermic men) showed that the majority of microdeletions occurred in men with sperm concentrations ≤ 1 million sperm/mL, with < 1% identified in men with > 1 million sperm/mL [1630]. In this context, while an absolute threshold for clinical testing cannot be universally given, patients may be offered testing if sperm counts are < 5 million sperm/mL, but must be tested if ≤1 million sperm/mL.

With the contribution of the European Academy of Andrology (EAA) guidelines and the 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 [1636].

*11.3.6 **Imaging in infertile men***

In addition to physical examination, a scrotal US may be helpful in: (i) measuring testicular volume; (ii) assessing testicular anatomy and structure in terms of US patterns, thus detecting signs of testicular dysgenesis often related to impaired spermatogenesis (e.g., non-homogeneous testicular architecture and microcalcifications) and testicular tumours; and, (iii) finding indirect signs of obstruction (e.g., dilatation of rete testis, enlarged epididymis with cystic lesions, or absent vas deferens) [1549]. In clinical practice, Prader's orchidometer-derived testicular volume is considered a reliable surrogate of US-measured testicular volume, easier to perform and cost-effective [1548]. Nevertheless, scrotal US has a relevant role in testicular volume assessment when Prader's orchidometer is unreliable (e.g., large hydrocele, inguinal testis, epididymal enlargement/fibrosis, thickened scrotal skin; small testis, where the epididymis is large in comparison to the total testicular volume [1548, 1549]). Ultrasound patterns of testicular inhomogeneity [1637, 1638] is usually associated with ageing, although it has also been reported in association with testicular atrophy and fibrosis [1549]. A diagnostic testicular biopsy is not recommended when testicular inhomogeneity is detected [1637, 1638].

11.3.6.1 Scrotal US

Scrotal US is widely used in everyday clinical practice in patients with oligo-zoospermia or azoospermia, as infertility has been found to be an additional risk factor for testicular cancer [1639, 1640]. It can be used in the diagnosis of several diseases causing infertility including obstructive azoospermia (see section 11.4), testicular neoplasms and varicocele.

11.3.6.1.1 Testicular neoplasms

In one study, men with infertility had an increased risk of testicular cancer (hazard ratio [HR] 3.3). When infertility was refined according to individual semen parameters, oligozoospermic men had an increased risk of cancer compared with fertile control subjects (HR 11.9) [1641]. In a recent systematic review infertile men with testicular microcalcification (TM) were found to have a ~18-fold higher prevalence of testicular cancer [1642]. The utility of US as a routine screening tool in men with infertility to detect testicular cancer remains a matter of debate [1639, 1640].

Indeed, these testicular lesions are difficult to characterise as being benign or malignant based only upon US criteria, including size, vascularity and echogenicity.

A dichotomous cut-off of certainty in terms of lesion size that may definitely distinguish benign from malignant testicular masses is currently not available. A systematic review and meta-analysis was carried out by the Testicular Cancer and the Sexual and reproductive health EAU Guidelines panels to to define which scrotal US or magnetic resonance imaging (MRI) characteristics can predict benign or malignant disease in pre- or post-pubertal males with indeterminate testicular masses [1643]. Benign and malignant masses were classified using the reported reference test: i.e., histopathology, or 12 months progression-free radiological surveillance. A total of 32 studies were identified, including 1692 masses of which 28 studies and 1550 masses reported scrotal US features, four studies and 142 masses reported MRI features. Meta-analysis of different scrotal US (B-mode) values in post-pubertal men demonstrated that a size of ≤0.5 cm had a significantly lower OR of malignancy compared to masses of >0.5 cm ($p < 0.001$). Comparison of masses of 0.6-1.0 cm and masses of > 1.5 cm also demonstrated a significantly lower OR of malignancy ($p = 0.04$). There was no significant difference between masses of 0.6-1.0 and 1.1-1.5 cm. Scrotal US in post-pubertal men also had a significantly lower OR of malignancy for heterogenous masses compared to homogenous masses ($p = 0.04$), hyperechogenic vs. hypoechogenic masses ($p < 0.01$), normal vs. increased enhancement ($p < 0.01$), and peripheral vs. central vascularity ($P < 0.01$), respectively. There were limited data on pre-pubertal SUS, pre-pubertal MRI and post-pubertal MRI [1643].

Small hypoechoic/hyperechoic areas may be diagnosed as intra-testicular cysts, focal Leydig cell hyperplasia, fibrosis and focal testicular inhomogeneity after previous pathological conditions. Hence, they require careful periodic US assessment and follow-up, especially if additional risk factors for malignancy are present (i.e., infertility, bilateral TM, history of cryptorchidism, testicular atrophy, inhomogeneous parenchyma, history of testicular tumour, history of/contralateral tumour) [1549].

In the case of interval growth of a lesion and/or the presence of additional risk factors for malignancy, testicular biopsy/surgery may be considered, although the evidence for adopting such a management policy is limited. In 145 men referred for azoospermia who underwent US before testicular biopsy, 49 (34%) had a focal US abnormality; a hypoechoic lesion was found in 20 patients (14%), hyperechoic lesions were seen in 10 patients (7%); and, a heterogeneous appearance of the testicular parenchyma was seen in 19 patients (13%). Of 18 evaluable patients, 11 had lesions < 5 mm; all of which were confirmed to be benign. All other patients with hyperechoic or heterogeneous areas on US with subsequent tissue diagnoses were found to have benign lesions. The authors concluded that men with severe infertility who have incidental testicular lesions, negative tumour markers and lesions < 5 mm may be observed with serial scrotal US examinations and enlarging lesions or those of greater dimension can be considered for histological biopsy [1644].

Other studies have suggested that if a testicular lesion is hyperechoic and non-vascular on colour Doppler US and associated with negative tumour markers, the likelihood of malignancy is low and consideration can be given to regular testicular surveillance, as an alternative to radical surgery. In contrast, hypoechoic and vascular lesions are more likely to be malignant [1645-1649]. However, most lesions cannot be characterised by US (indeterminate), and histology remains the only certain diagnostic tool. A multidisciplinary team discussion (MDT), including invasive diagnostic modalities, should therefore be considered in these patients.

The role of US-guided intra-operative frozen section analysis in the diagnosis of testicular cancer in indeterminate lesions can be considered, and several authors have proposed its value in the intra-operative diagnosis of indeterminate testicular lesions [1650]. Although the default treatment after patient counselling and MDT discussion may be radical orchidectomy, an US-guided biopsy with intra-operative frozen section analysis may be offered as an alternative to radical orchidectomy and potentially obviate the need for removal of the testis in a patient seeking fertility treatment. In men with azoospermia a concurrent TESE with sperm banking can also be performed at the time of surgical intervention.

11.3.6.1.2 Varicocele

At present, the clinical management of varicocele is still mainly based on physical examination; nevertheless, scrotal colour Doppler US is useful in assessing venous reflux and diameter, when palpation is unreliable and/or in detecting recurrence/persistence after surgery [1549]. Definitive evidence of reflux and venous diameter may be utilised in the decision to treat (see Section 11.4.3.1 and 11.4.3.2).

11.3.6.1.3 Other

Scrotal US is able to detect changes in the proximal part of the seminal tract due to obstruction. Especially for CBAVD patients, scrotal US is a favourable option to detect the abnormal appearance of the epididymis. Given that, three types of epididymal findings are described in CBAVD patients: tubular ectasia (honeycomb appearance), meshwork pattern, and complete or partial absence of the epididymis [1651, 1652].

11.3.6.2 Transrectal US

For patients with a low seminal volume, acidic pH and severe oligozoospermia or azoospermia, in whom obstruction is suspected, scrotal and transrectal US are of clinical value in detecting CBAVD and presence or absence of the epididymis and/or seminal vesicles (SV) (e.g., abnormalities/agenesis). Likewise, transrectal US (TRUS) has an important role in assessing obstructive azoospermia (OA) secondary to CBAVD or anomalies related to the obstruction of the ejaculatory ducts, such as ejaculatory duct cysts, seminal vesicle dilatation or hypoplasia/atrophy, although retrograde ejaculation should be excluded as a differential diagnosis [1549, 1653].

*11.3.7 **Summary of evidence and recommendations for the diagnostic work-up of male infertility***

Summary of evidence	**LE**
Semen analysis alone cannot distinguish fertile from infertile men.	2a
Diagnosis of male infertility is associated with an increased risk of death and comorbidities.	2a
Male infertility evaluation should include a medical, reproductive and family history, assessment of lifestyle and behavioural risk factors, physical examination, semen analysis and hormonal evaluation.	2a
Genetic analysis and imaging may be required depending on the clinical features and semen parameters.	2a
Testicular volume can be measured with a Prader orchidometer or using testicular ultrasound.	2a
Semen analyses is described in the latest edition of the WHO Manual for the Examination and Processing of Human Semen. Abnormal semen characteristics are expressed as below the 5th percentiles of a reference population of 3500 men who contributed to a natural conception within 12 months.	3
Oxidative stress has a detrimental impact on sperm quality but there is a lack of validated assays to measure ROS and oxidative stress in the evereday clinical practice.	2b
High sperm DNA fragmentation index (SDF) is associated with reduced pregnancy rates via natural conception or intra-uterine insemination, poor assisted reproductive techniques (ART) outcomes, recurrent pregnancy loss and unexplained infertility.	2a
A possible advantage of the use of testicular sperm for ICSI in patients with high SDF in ejaculated sperm has not been confirmed in large scale RCTs.	3
Gonadotropins and total testosterone measurement are useful to diagnose testicular deficiency and to classify the type of hypogonadism.	2a
Follicle-stimulating hormone values have been negatively associated with sperm count.	2a
Chromosomal abnormalities are frequently found in men with severe oligozoospermia (spermatozoa <5 million/mL) or azoospermia.	2a
Klinefelter syndrome is associated with non-obstructive azoospermia, hypogonadism and general health problems, including metabolic, cardiovascular and oncologic diseases.	2a
Cystic fibrosis transmembrane conductance regulator (CFTR) gene mutations may be associated with congenital bilateral absence of the vas deferens CBAVD and obstructive azoospermia.	2a
The prevalence of renal anomalies is rare for patients with unilateral and bilateral absence of the vas deferens and CFTR mutations.	2a
The highest frequency of Y-microdeletions is found in azoospermic men followed by oligospermic men but is extremely rare with a sperm concentration > 5 million/mL.	2a
Complete deletions that include the AZFa and AZFb regions are of poor prognostic significance for retrieving sperm with surgery.	2a
Testicular sperm can be found in 50-75% of men with AZFc microdeletions.	2a
Male offspring of men with AZF microdeletions will inherit the deletion.	2a
Genetic abnormalities found during the diagnostic work-up might impact on the psychological and overall health of the couple and the offspring.	2a
Scrotal ultrasound is used to measure testicular volume, assess testicular anatomy including detecting signs of obstruction and testicular dysgenesis.	2a
Infertile men have a higher risk of testicular cancer compared to fertile controls.	2a
An essential approach for infertile men with US-detected indeterminate testicular lesion is a multidisciplinary discussion with focus on the size of the lesion, echogenicity, vascularity and previous patient's history (e.g., cryptorchidism, previous history of germ cell tumour [GCT]).	2a

Scrotal ultrasound is useful in assessing venous reflux and diameter of the spermatic vein, mostly when palpation is unreliable or in detecting recurrence/persistence after surgery	2a
In patients with a low seminal volume, acidic pH and either severe oligozoospermia or azoospermia in the absence of CBAVD, transrectal ultrasound should be used to detect complete or partial ejaculatory duct obstruction	2b

Recommendations	Strength rating
Include a parallel assessment of the fertility status, including ovarian reserve, of the female partner during the diagnosis and management of the infertile male, since this might determine decision making in terms of timing and therapeutic strategies (e.g., assisted reproductive technology (ART) versus surgical intervention).	Strong
Examine all men seeking medical help for fertility problems, including men with abnormal semen parameters.	Strong
Take a complete medical reproductive and family history, assessment of lifestyle and behaviour risk factors, physical examinationand semen analysis	Strong
Counsel infertile men or men with abnormal semen parameters on the associated health risks.	Weak
Assess testicular volume with a Prader's orchidometer or testicular ultrasound (US).	Weak
Perform semen analyses according to the latest edition of the WHO Manual for the Examination and Processing of Human Semen. Perform at least two consecutive semen analyses if the baseline analysis was abnormal.	Strong
Do not routinely use reactive oxygen species (ROS) testing in the diagnosis and management of the male partner of an infertile couple.	Weak
Perform sperm DNA fragmentation (SDF) testing in the assessment of couples with recurrent pregnancy loss from natural conception and failure of ART or men with unexplained infertility.	Strong
Consider the use of testicular sperm for ICSI in patients with high SDF in ejaculated sperm as experimental	Weak
Perform a hormonal evaluation including serum total testosterone and Follicle Stimulating Hormone/Luteinising Hormone at least in all cases of oligozoospermia and azoospermia.	Strong
Offer standard karyotype analysis and genetic counselling to all men with azoospermia and oligozoospermia (spermatozoa < 5 million/mL) for diagnostic purposes.	Strong
Provide long-term endocrine follow-up and appropriate medical treatment to men with Klinefelter syndrome.	Strong
Perform Y-chromosome microdeletion testing in men with sperm concentrations of ≤ 1 million sperm/mL. Considerit in men with sperm concentrations of < 5 million sperm/mL.	Strong
Inform men with Yq microdeletion and their partners who wish to proceed with intra-cytoplasmic sperm injection (ICSI) that microdeletions will be passed to sons.	Strong
Do not perform testicular sperm extraction in patients with complete deletions that include the AZFa and AZFb regions.	Strong
Test men with structural abnormalities of the vas deferens (unilateral or bilateral absence with no renal anomalies) and their partners for cystic fibrosis transmembrane conductance regulator gene mutations.	Strong
Provide genetic counselling in all couples with a genetic abnormality found on clinical or genetic investigation and in patients who carry a (potential) inheritable disease.	Strong
Perform scrotal US in patients with infertility, as there is a higher risk of testis cancer.	Weak
Discuss invasive diagnostic modalities (e.g., US-guided testicular biopsy with frozen section versus radical orchidectomy versus surveillance) in infertile men with US-detected indeterminate testicular lesions, especially if additional risk factors for malignancy are present in a multidisciplinary team setting.	Weak
Perform transrectal US if a partial or complete distal obstruction is suspected.	Strong

11.4 Special Conditions and Relevant Clinical Entities

*11.4.1 **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 [1654]. Approximately 30% of undescended testes are non-

palpable and may be located within the abdominal cavity. These guidelines will only deal with management of cryptorchidism in adults.

11.4.1.1 Classification

The classification of cryptorchidism is based on the duration of the condition and the anatomical position of the testes. If the undescended testis has been identified from birth then it is termed congenital while diagnosis of acquired cryptorchidism refers to men in whom testes were situated within the scrotum. Cryptorchidism is categorised as bilateral or unilateral and the location of the testes (inguinal, intra-abdominal or ectopic).

Studies have shown that treatment of congenital and acquired cryptorchidism results in similar hormonal profiles, semen analysis and testicular volumes [1655, 1656]. However, testicular volume and hormonal function are reduced in adults treated for congenital bilateral cryptorchidism compared to unilateral cryptorchidism [1657].

11.4.1.1.1 etiology 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, including exposure to endocrine disrupting chemicals. Besides cryptorchidism, TDS includes hypospadias, reduced fertility, increased risk of malignancy, and Leydig/Sertoli cell dysfunction [1658]. Cryptorchidism has also been linked with maternal gestational smoking [1659] and premature birth [1660].

11.4.1.1.2 Pathophysiological effects in maldescended testes

11.4.1.1.2.1 Degeneration of germ cells

The degeneration of germ cells in maldescended testes is apparent even after the first year of life and varies, depending on the position of the testes [1661]. During the second year, the number of germ cells declines further. Treatment between the age of six to 18 months is therefore recommended to conserve spermatogonial stem cells, safe guard future spermatogenesis and hormone production, as well as to decrease the risk for tumours [1662]. Surgical treatment is the most effective. Meta-analyses on the use of medical treatment with GnRH and hCG have demonstrated poor success rates [1663, 1664]. It has been reported that hCG treatment may be harmful to future spermatogenesis [1665]. The EAU Guidelines on Paediatric Urology do not recommend endocrine treatment to achieve testicular descent on a routine basis, but endocrine treatment with GnRH analogues in boys with bilateral undescended testis is recommended [1666].

There is increasing evidence to suggest that in unilateral undescended testis, the contralateral normal descended testis may also have structural abnormalities, including smaller volume, softer consistency and reduced markers of future fertility potential (spermatogonia/tubule ratio and dark spermatogonia) [1655, 1667]. This implies that unilateral cryptorchidism may affect the contralateral testis and patients and parents should be counselled appropriately.

11.4.1.1.2.2 Relationship with fertility

Semen parameters are often impaired in men with a history of cryptorchidism [1668]. Early surgical treatment may have a positive effect on subsequent fertility [1669]. In men with a history of unilateral cryptorchidism, paternity is almost equal (89.7%) to that in men without cryptorchidism (93.7%). Outcome studies for untreated bilateral undescended testes revealed that 100% are oligospermic and 75% azoospermic men. Among those successfully treated for bilateral undescended testes, 75% still remain oligospermic and 42% azoospermic [1670]. It is also important to screen for hypogonadism, as this is a potential long-term sequelae of cryptorchidism and could contribute to impaired fertility and potential problems such as testosterone deficiency and MetS [1671].

11.4.1.1.2.3 Germ cell tumours

As a component of TDS, cryptorchidism is a risk factor for testicular cancer and is associated with testicular microcalcifications and intratubular germ cell neoplasia *in situ* (GCNIS), formerly known as carcinoma *in situ* (CIS) of the testes. In 5-10% of testicular cancers, there is a history of cryptorchidism [1672]. The risk of a germ cell tumour 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 [1654]. Orchidopexy performed before the onset of puberty has been reported to decrease the risk of testicular cancer [1673]. However, there is evidence to suggest that even men who undergo early orchidopexy still harbour a higher risk of testicular cancer than men without cryptorchidism [1674]. Therefore, all men with a history of cryptorchidism should be warned that they are at increased risk of developing testicular cancer and should perform regular testicular self-examination [1675].

11.4.1.2 Disease management

11.4.1.2.1 Hormonal treatment

Human chorionic gonadotropin or GnRH is not recommended for the treatment of cryptorchidism in adulthood.

11.4.1.2.2 Surgical treatment

In adolescence, removal of an intra-abdominal testis (with a normal contralateral testis) can be recommended, because of the risk of malignancy [1676]. In adults, with a palpable undescended testis and a normal functioning contralateral testis (i.e., biochemically eugonadal), an orchidectomy may be offered as there is evidence that the undescended testis confers a higher risk of GCNIS and future development of a GCT [1677] and regular testicular self-examination is not an option in these patients. In patients with unilateral undescended testis and impaired testicular function on the contralateral testis as demonstrated by biochemical hypogonadism and/or impaired sperm production (infertility), an orchidopexy may be offered to preserve androgen production and fertility. However, based on Panel consensus multiple biopsies of the unilateral undescended testis are recommended at the time of orchidopexy to exclude intra-testicular GCNIS as a prognostic indicator of future development of GCT. As indicated above, the correction of bilateral cryptorchidism, even in adulthood, can lead to sperm production in previously azoospermic men and therefore may be considered in these patients or in patients who place a high value on fertility preservation [1678]. Vascular damage is the most severe complication of orchidopexy and can cause testicular atrophy in 1-2% of cases. In men with non-palpable testes, the post-operative atrophy rate was 12% in cases with long vascular pedicles that enabled scrotal positioning. Post-operative atrophy in staged orchidopexy has been reported in up to 40% of patients [1679]. At the time of orchidectomy in the treatment of GCT, biopsy of the contralateral testis should be offered to patients at high risk for GCNIS (i.e., history of cryptorchidism, < 12 mL testicular volume, poor spermatogenesis [1680]).

11.4.1.3 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 GCTs and patients should be counselled appropriately.	2b
Paternity in men with corrected unilateral cryptorchidism is almost equal to men without cryptorchidism.	1b
Bilateral cryptorchidism significantly reduces the likelihood of paternity and patients should be counselled appropriately.	1b

Recommendations	**Strength rating**
Do not use hormonal treatment for cryptorchidism in post-pubertal men.	Strong
Perform simultaneous testicular biopsy, for the detection of intratubular germ cell neoplasia *in situ* (formerly carcinoma *in situ*), if undescended testes are corrected in adulthood.	Strong
Offer adult men with unilateral undescended testis and normal hormonal function/spermatogenesis orchidectomy.	Strong
Offer adult men with unilateral or bilateral undescended testis with biochemical hypogonadism and or spermatogenic failure (i.e., infertility) unilateral or bilateral orchidopexy, if technically feasible.	Weak

11.4.2 ***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 sub-fertile men [1681]. The lifetime risk of TGCT varies among 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 GCNIS, and untreated GCNIS eventually progresses to invasive cancer [1682-1684]. There has been a general decline in male reproductive health and an increase in testicular cancer in western countries [1685, 1686]. In almost all countries with reliable cancer registries, the incidence of testicular cancer has increased [1635, 1687]. This has been postulated to be related to TDS, which is a developmental disorder of the testes caused by environmental and/or genetic influences in pregnancy. Endocrine disrupting chemicals have also been associated with sexual dysfunction [1688] and abnormal semen parameters [1689]. These

cancers arise from premalignant gonocytes or GCNIS [1690]. Testicular microcalcification, seen on US, can be associated with TGCT and GCNIS of the testes [1642, 1691, 1692].

11.4.2.1 Testicular germ cell cancer and reproductive function

All men with cancer must be offered sperm cryopreservation prior to the therapeutic use of gonadotoxic agents or ablative surgery that may impair spermatogenesis or ejaculation (i.e., chemotherapy, radiotherapy or retroperitoneal surgery) [1693, 1694].

Men with TGCT have decreased semen quality, even before cancer treatment. Azoospermia has been observed in 24% of men with TGCT [1695] and oligospermia in 50% [1696]. Given that the average ten-year survival rate for testicular cancer is 98% and it is the most common cancer in men of reproductive potential, it is mandatory to include counselling regarding fertility preservation prior to any gonadotoxic treatment [1696, 1697]. All patients should be offered ejaculated semen preservation as the most cost-effective strategy for fertility preservation, or sperm extracted surgically (e.g., c/mTESE). Indeed, treatment for TGCT, including orchidectomy because of the risk of a non-functioning remaining testicle, may have a negative impact on reproductive function [1695]. If shown to be azoospermic or severely oligozoospermic, it is recommended that men should undergo sperm cryopreservation prior to orchidectomy to allow an opportunity to perform a concomitant TESE and prior to further potential gonadotoxic/ablative surgery [1696]. The surgical principles in onco-TESE do not differ from the technique of TESE for men with infertility (e.g., NOA) [1698, 1699]. In this context, it is recommended to organise cryopreservation care delivery networks that enables referral to a urologist adept in TESE.

Rates of under-utilisation of semen analysis and sperm cryopreservation have been reported to be high; resulting in the failure to identify azoospermic or severely oligozoospermic patients at diagnosis who may benefit from advanced fertility-preserving procedures such as oncoTESE. The argument that performing cryopreservation prior to orchidectomy may delay subsequent treatment is not supported by contemporary clinical practice, indeed adverse impact on survival has not been investigated. In this context, orchidectomy should not be unduly delayed if there are no facilities for cryopreservation or there is a potential delay in treatment.

Since chemotherapy and RT are teratogenic, contraception must be used during treatment and for at least six months after completion [1700]. Both chemotherapy and RT can impair fertility. Long-term infertility is rare after RT and dose-cumulative-dependent with chemotherapy. Treatment of TGCT can result in additional impairment of semen quality [1701] and increased sperm aneuploidy up to two years following gonadotoxic therapy [1702]. Spermatogenesis usually recovers one to four years after chemotherapy [74]. Chemotherapy is also associated with DNA damage and an increased SDF rate [1703]. However, sperm aneuploidy levels often decline to pre-treatment levels 18-24 months after treatment [1702]. Several studies reviewing the offspring of cancer survivors have not shown a significant increased risk of genetic abnormalities in the context of previous chemotherapy and radiotherapy [1704].

In addition to spermatogenic failure, patients with TGCT have Leydig cell dysfunction, even in the contralateral testis [1705]. The measurement of pre-treatment levels of testosterone, SHBG, LH and oestradiol may help to stratify those patients at increased risk of hypogonadism and provide a baseline for post-treatment hypogonadism. The risk of hypogonadism may be increased in men treated for TGCT. Likewise, the risk of hypogonadism is increased in the survivors of testicular cancer and serum testosterone levels should be evaluated during the management of these patients [1706]. However, this risk is greatest at 6-12 months post-treatment and suggests that there may be some improvement in Leydig cell function after treatment. Therefore, it is reasonable to delay initiation of testosterone therapy, until the patient shows continuous signs or symptoms of testosterone deficiency [1682]. The risk of low libido and erectile dysfunction is also increased in TGCT patients [1707]. Patients treated for TGCT are also at increased risk of CVD [1703]. Therefore, patients may require a multi-disciplinary therapy approach and, in this context, survivorship programmes incorporating a holistic view of patients considering psychological, medical and social needs could be beneficial. In patients who place a high value on fertility potential, the use of testosterone therapy in men with symptoms suggestive for TDS needs to be balanced with worsening spermatogenesis. In these patients consideration can be given to the use of selective oestrogen receptor modulators (SERMs; e.g., clomiphene) or gonadotrophin analogues (e.g., hCG), although these are off-label treatments in this particular clinical setting.

11.4.2.2 Testicular microcalcification (TM)

Microcalcification inside the testicular parenchyma can be found in 0.6-9% of men referred for testicular US [1708, 1709]. Although the true incidence of TM in the general population is unknown, it is most probably rare. Ultrasound findings of TM have been seen in men with TGCT, cryptorchidism, infertility, testicular torsion

and atrophy, Klinefelter syndrome, hypogonadism, Disorders of Sex Development and varicocele [1659]. The incidence reported seems to be higher with high-frequency US machines [1710]. The relationship between TM and infertility is unclear, but may relate to testicular dysgenesis, with degenerate cells being sloughed inside an obstructed seminiferous tubule and failure of the Sertoli cells to phagocytose the debris. Subsequently, calcification with hydroxyapatite occurs. Testicular microcalcification is found in testes at risk of malignant development, with a reported incidence of TM in men with TGCT of 6-46% [1711-1713]. A systematic review and meta-analysis of case-control studies indicated that the presence of TM is associated with a ~18-fold higher odds ratio for testicular cancer in infertile men (pooled OR: 18.11, 95% CI: 8.09, 40.55; $p < 0.0001$) [1642].

Testicular microcalcification should therefore be considered pre-malignant in this setting and patients counselled accordingly. Testicular biopsies from men with TM have found a higher prevalence of GCNIS, especially in those with bilateral microcalcifications [1714]. However, TM can also occur in benign testicular conditions and the microcalcification itself is not malignant. Therefore, the association of TM and TGCT is controversial and the challenge is to identify those men at risk of harbouring GCNIS and future risk of TGCT. Further investigation of the association between TM and GCNIS requires testicular biopsies in large series of men without signs of TGCT with or without risk factors for TGCT. However, clinicians and patients should be reassured that testicular cancer does not develop in most men with asymptomatic TM [1692]. Men potentially at high-risk of harbouring or developing GCNIS include those with infertility, atrophic testes, undescended testes, history of TGCT, and contralateral TM and it has been suggested that men with these risk factors could be offered testicular biopsy [1686, 1691]. Patients with a history of TGCT and TM in the contralateral testis and sub-fertile patients have been demonstrated to have an increased risk of GCNIS [1692], while there are only a few studies showing a further increase in GCNIS with TM in the context of cryptorchidism [1686, 1709, 1715]. A useful algorithm has been proposed [1686] to stratifying those patients at increased risk of GCNIS who may benefit from testicular biopsy. However, when undertaking a biopsy in this setting, the full risks and complications of adopting this strategy must be explained to the patient.

Decastro *et al.,* [1716] suggested that testicular cancer would not develop in most men with TM (98.4%) during a five-year follow-up. As such, an extensive screening programme would only benefit men at significant risk. In this context it would be prudent to advise patients with TM and risk factors for testicular cancer to at least undergo regular testicular examination. It has been suggested that these patients could also be offered annual physical examination by a urologist and US follow-up, although follow-up protocols may be difficult to implement in this invariably young cohort of patients [1659]. As testicular atrophy and infertility have an association with testicular cancer, some authors recommend biopsy or follow-up US if TM is seen [1686]. However, most patients who are azoospermic will be undergoing therapeutic biopsy (i.e., with the specific purpose of sperm retrieval) and therefore a definitive diagnosis can be made and there is a lack of evidence demonstrating a higher prevalence of testicular cancer in patients with both TM and testicular atrophy. In patients with incidental TM, the risk of GCNIS is low and a logical approach is to instruct patients to perform regular testicular self-examination.

11.4.2.3 Summary of evidence and recommendations for germ cell malignancy and testicular microcalcification

Summary of evidence	**LE**
Testicular germ cell tumour (TGCT) affects approximately 1% of sub-fertile men.	2b
Men with TGCT frequently have impaired sperm parameters at diagnosis.	2a
Semen analysis and sperm cryopreservation before orchidectomy allows the identification of TGCT patients with azoospermia, who may benefit from concomitant surgical sperm retrieval (i.e., onco-TESE).	2b
Treatment of TGCT can result in decreased sperm quality, sperm aneuploidy, increased sperm DNA fragmentation (SDF), hypogonadism, sexual dysfunction and cardiovascular diseases.	2a
Testicular microcalcifications (TM) can be found in men with benign conditions (e.g., cryptorchidism, infertility, testicular torsion and atrophy, Klinefelter syndrome, hypogonadism, DSD, varicocele) and (pre)malignant (GCNIS) or malignant conditions (TGCT).	2a
Testicular microcalcifications are associated with a higher risk of testicular cancer in infertile men.	1a
Men potentially at risk for harbouring or developing GCNIS include those with bilateral TM, infertility, atrophic testes, undescended testes, history of TGCT, and contralateral TM.	2a
Since TGCT will not develop in most men with TM, an extensive screening programme or invasive testicular biopsy is not indicated without additional risk factors.	2b

Recommendations	Strength rating
Advise men with testicular microcalcification (TM) to perform self-examination even without additional risk factors, as this may result in early detection of a testicular germ cell tumour (TGCT).	Weak
Do not perform testicular biopsy, follow-up scrotal ultrasound (US), measure biochemical tumour markers, or abdominal or pelvic computed tomography, in men with isolated TM without associated risk factors (e.g., infertility, cryptorchidism, testicular cancer, and atrophic testis).	Strong
Offer testicular biopsy to infertile men with TM, who belong to one of the following higher risk groups: spermatogenic failure (infertility), bilateral TM, atrophic testes (< 12 mL), history of undescended testes and TGCT.	Weak
Perform inguinal surgical exploration with testicular biopsy or offer orchidectomy after multi-disciplinary team meeting and discussion with the patient, if there are suspicious findings on physical examination or US in patients with TM with associated lesions.	Strong
Manage men treated for TGCT in a multi-disciplinary team setting with a dedicated late-effects clinic and survivorship program, since they are at increased risk of developing hypogonadism, sexual dysfunction and cardiovascular risk.	Strong
Perform sperm cryopreservation prior to planned orchidectomy or before additional neoadjuvant or adjuvant oncological therapies.	Strong
Offer onco-testicular sperm extraction (onco-TESE) at the time of radical orchidectomy in men with testicular cancer and azoospermia or severe abnormalities in their semen parameters.	Strong

*11.4.3 **Varicocele***

Varicocele is a common congenital abnormality, that may be associated with the following andrological conditions:

- failure of ipsilateral testicular growth and development;
- male sub-fertility;
- symptoms of pain and discomfort;
- hypogonadism.

11.4.3.1 Classification

The following classification of varicocele [1522] is useful in clinical practice:

- Subclinical: not palpable or visible at rest or during Valsalva manoeuvre, but can be shown by special tests (Doppler US).
- Grade 1: palpable during Valsalva manoeuvre.
- Grade 2: palpable at rest.
- Grade 3: visible and palpable at rest.

11.4.3.2 Diagnostic evaluation

The diagnosis of varicocele is made by physical examination and Scrotal Doppler US is indicated if physical examination is inconclusive or semen analysis remains unsatisfactory after varicocele repair to identify persistent and recurrent varicocele [1522, 1717]. A maximum venous diameter of > 3 mm in the upright position and during the Valsalva manoeuvre and venous reflux with a duration > 2 seconds correlate with the presence of a clinically significant varicocele [1718, 1719]. To calculate testicular volume Lambert's formula (V=L x W x H x 0.71) should be used, as it correlates well with testicular function in patients with infertility and/or varicocele [1720]. Patients with isolated, clinical right varicocele should be examined further for abdominal, retroperitoneal and congenital pathology and anomalies.

11.4.3.3 Basic considerations

11.4.3.3.1 Varicocele and fertility

Varicocele is present in almost 15% of the normal male population, in 25% of men with abnormal semen analysis and in 35-40% of men presenting with infertility [1522, 1721-1723]. The incidence of varicocele among men with primary infertility is estimated at 35–44%, whereas the incidence in men with secondary infertility is 45–81% [1522, 1722, 1723]. Worsening semen parameters are associated with a higher grade of varicocele and age [1722, 1724].

The exact association between reduced male fertility and varicocele is unknown. Increased scrotal temperature, hypoxia and reflux of toxic metabolites can cause testicular dysfunction and infertility due to increased overall survival and DNA damage [1723].

The exact association between reduced male fertility and varicocele is unknown. Increased scrotal temperature, hypoxia and reflux of toxic metabolites can cause testicular dysfunction and infertility due to increased [1721, 1723].

11.4.3.3.2 Varicocelectomy

Varicocele repair has been a subject of debate for several decades. A meta-analysis of RCTs and observational studies in men with only clinical varicoceles has shown that surgical varicocelectomy significantly improves semen parameters in men with abnormal semen parameters, including men with NOA with hypo-spermatogenesis or late maturation (spermatid) arrest on testicular pathology [1721, 1725-1728]. A meta-analysis showed that improvements in semen parameters are usually observed after surgical correction in men with abnormal semen parameters [1729]. Varicocelectomy can also reverse sperm DNA damage and improve OS levels [1721, 1723]. Pain resolution after varicocelectomy occurs in 48-90% of patients [1730]. A systematic review has shown greater improvement in higher-grade varicoceles and this should be taken into account during patient counselling [1731].

In RCTs, varicocele repair in men with a subclinical varicocele was ineffective at increasing the chances of spontaneous pregnancy [1732]. Also, in randomised studies that included mainly men with normal semen parameters no benefit was found to favour treatment over observation. This was also reported in a systematic review and meta-analysis including prospective randomised and non-randomised studies [1733]. In studies including patients with abnormal semen parameters pregnancy rates (OR 1.29, 95% CI 1.00–1.65, p = 0.04) and total sperm count (mean difference: 12.34 million/ml, 95% CI 3.49–21.18, p = 0.006) were significantly improved by varicocele treatment compared with observation. A benefit for varicocele treatment was not found for sperm progressive motility and normal sperm morphology [1733]. When pre- versus post-treatment values were considered in the varicocele treatment arm only a benefit in terms of sperm count, progressive motility, and normal morphology was found [1733]. Another systematic review and meta-analysis evaluated the change in conventional semen parameters after varicocele repair (n=1,426) compared to untreated controls (n=996) [1734]. Significantly improved post-operative semen parameters where reported in treated patients compared to controls with regards to sperm concentration (SMD 1.73; 95% CI 1.12 to 2.34; p<0.001), total sperm count (SMD 1.89; 95% CI 0.56 to 3.22; p < 0.05), progressive sperm motility (SMD 3.30; 95% CI 2.16 to 4.43; p < 0.01), total sperm motility (SMD 0.88; 95% CI 0.03 to 1.73; p=0.04) and normal sperm morphology (SMD 1.67; 95% CI 0.87 to 2.47; p < 0.05) [1734].

A Cochrane review from 2012 concluded that there is evidence to suggest that treatment of a varicocele in men from couples with otherwise unexplained subfertility may improve a couple's chance of spontaneous pregnancy [1735]. Similarly, a Cochrane review from 2021 including 5,384 participants showed that varicocele treatment may improve pregnancy rates compared to delayed or no treatment (RR 1.55, 95% CI 1.06 to 2.26) [1736]. Two meta-analyses of RCTs comparing treatment to observation in men with a clinical varicocele, oligozoospermia and otherwise unexplained infertility, favoured treatment, with a combined OR of 2.39-4.15 (95% CI: 1.56-3.66) and (95% CI: 2.31-7.45), respectively [1728, 1735]. Average time to improvement in semen parameters is up to two spermatogenic cycles [1737, 1738] with spontaneous pregnancy occurring between six and twelve months after varicocelectomy [1739, 1740]. A further meta-analysis has reported that varicocelectomy may improve outcomes following ART in oligozoospermic men with an OR of 1.69 (95% CI: 0.95-3.02) [1741].

11.4.3.3.3 Prophylactic varicocelectomy

In adolescents with a varicocele, there is a significant risk of over-treatment because most adolescents with a varicocele have no problem achieving pregnancy later in life [1742]. Prophylactic treatment is only advised in case of documented testicular growth deterioration confirmed by serial clinical or Doppler US examinations and/or abnormal semen analysis [1743, 1744].

Varicocelectomy and NOA

Several non-randomised studies have suggested that varicocelectomy may lead to sperm appearing in the ejaculate in men with azoospermia. In one such study, microsurgical varicocelectomy in men with NOA led to sperm in the ejaculate post-operatively with an increase in ensuing natural or assisted pregnancies [1745]. Meta-analyses have further corroborated these findings; 468 patients diagnosed with NOA and varicocele underwent surgical varicocele repair or percutaneous embolisation. In patients who underwent varicocelectomy, SRRs increased compared to those without varicocele repair (OR: 2.65; 95% CI: 1.69-4.14; p < 0.001). In 43.9%

of the patients (range: 20.8%-55.0%), sperm were found in post-operative ejaculate. These findings indicate that varicocelectomy in patients with NOA and clinical varicocele is associated with improved SRR, that sperm retrieval may be avoided when sperm reappear in the ejaculate following varicocelectomy. However, the quality of evidence available is low and the risks and benefits of varicocele repair must be discussed fully with the patient with NOA and a clinically significant varicocele prior to embarking upon treatment intervention [1726]. The current understanding of the underlying genetic defects of NOA must be taken into account when interpreting contemporary literature.

Varicocelectomy and hypogonadism
Evidence also suggests that men with clinical varicoceles who are hypogonadal may benefit from varicocele intervention. One meta-analysis studied the efficacy of varicocele intervention by comparing the pre-operative and post-operative serum testosterone of 712 men. The combined analysis of seven studies demonstrated that the mean post-operative serum testosterone improved by 34.3 ng/dL (95% CI: 22.57-46.04, $p < 0.00001$, $I^2 = 0\%$) compared with their pre-operative levels. An analysis of surgery vs. untreated control results showed that mean testosterone among hypoganadal patients increased by 105.65 ng/dL (95% CI: 77.99-133.32 ng/dL), favouring varicocelectomy [1746]. However, results must be treated with caution and adequate cost-benefit analysis must be undertaken to determine the risks and benefits of surgical intervention over testosterone therapy in this setting. Although, varicocelectomy may be offered to hypogonadal men with clinically significant varicoceles, patients must be advised that the full benefits of treatment in this setting must be further evaluated with prospective RCTs.

11.4.3.3.4 Varicocelectomy for assisted reproductive technology and raised SDF
Varicocelectomy can improve sperm DNA integrity [1742, 1747]. A systematic review and meta-analysis analysed data from 1,070 infertile men with clinical varicocele and showed that varicocelectomy was associated with reduced post-operative SDF rates (weighted mean difference 7.23%; 95% CI: 8.86 to 5.59) [1748]. Improvement of DNA integrity was independent from the assay used (SCSA vs. TUNEL vs. SCD) and the surgical technique performed. The estimated weighted mean difference was greater in studies with pre-operative mean fragmentation index ≥ 20% than that in studies with SDF < 20%, suggesting that varicocelectomy might be more beneficial in men with elevated baseline SDF values [1748]. The magnitude of the effect size increased as a function of preoperative SDF levels (coefficient: 0.23; 95%CI: 0.07 to 0.39).

There is now increasing evidence that varicocele treatment may improve DNA fragmentation and outcomes from ART [1741, 1742]. As a consequence, more recently it has been suggested that the indications for varicocele intervention should be expanded to include men with raised DNA fragmentation. If a patient has failed ART (e.g., failure of implantation, embryogenesis or recurrent pregnancy loss) there is an argument that if DNA damage is raised, consideration could be given to varicocele intervention after extensive counselling [1749], and exclusion of other causes of raised SDF [1742, 1750].The dilemma remains as to whether varicocele treatment is indicated in men with raised SDF and normal semen parameters. This decision would need a full and open discussion with the infertile couple, taking into consideration the female partners ovarian reserve and the surgical risks and potential delays in ART associated with varicocele intervention.

In a meta-analysis of non-azoospermic infertile men with clinical varicocele by Estevez *et al.*, four retrospective studies were included of men undergoing ICSI, and included 870 cycles (438 subjected to ICSI with prior varicocelectomy, and 432 without prior varicocelectomy). There was a significant increase in the clinical pregnancy rates (OR 1.59, 95% CI: 1.19-2.12, I2 = 25%) and live birth rates (OR 2.17, 95% CI: 1.55-3.06, I2 = 0%) in the varicocelectomy group compared to the group subjected to ICSI without previous varicocelectomy [1726]. A further study evaluated the effects of varicocele repair and its impact on pregnancy and live birth rates in infertile couples undergoing ART in male partners with oligo-azoospermia or azoospermia and a varicocele [1741]. In 1,241 patients, a meta-analysis demonstrated that varicocelectomy improved live birth rates for the oligospermic (OR = 1.699) men and combined oligo-azoospermic/azoospermic groups (OR = 1.761). Pregnancy rates were higher in the azoospermic group (OR = 2.336) and combined oligo-azoospermic/azoospermic groups (OR 1.760). Live birth rates were higher for patients undergoing IUI after intervention (OR 8.360).

11.4.3.4 Disease management
Several treatments are available for varicocele (Table 38).

Impact on pregnancy rate and semen parameters
Current evidence indicates that microsurgical varicocelectomy is the most effective among the different varicocelectomy techniques [1742, 1751]. A Cochrane review reported that microsurgical subinguinal varicocelectomy probably improves pregnancy rates slightly more compared to other surgical treatments (RR

1.18, 95% CI 1.02 to 1.36) [1736]. A subgroup analysis from a systematic review of prospective randomised and non-randomised studies reported that surgical approach (including all possible surgical techniques) significantly improved pregnancy rates and sperm concentration as compared with controls, while the same was not demonstrated for radiological treatment [1733]. However, the most recent Cochrane review showed inconclusive results about the effect of surgical vs. radiological treatment on pregnancy rates and varicocele recurrence [1736]. There are no large prospective RCTs comparing the efficacy of the various interventions for varicocele.

Complications

Microsurgical repair results in fewer complications and lower recurrence rates compared to the other techniques [1736, 1752, 1753]; however, this procedure, requires microsurgical training. The various other techniques are still considered viable options, although recurrences and hydrocele formation appear to be higher [1753].

Radiological techniques (sclerotherapy and embolisation) are minimally invasive approaches for varicocele treatment. Although higher recurrence rates have been reported compared to microscopic varicocelectomy [1754], a meta-analysis showed that the incidence of varicocele recurrence was similar after surgical ligation and sclero-embolisation [1754]. In terms of complications, a meta-analysis of twelve studies comparing 738 cases of surgical ligation vs. 647 cases of sclero-embolisation, showed that overall complications rate did not differ significantly between the groups (OR 1.48; 95% CI 0.86–2.57, p = 0.16) [1754]. The incidence of post-operative hydrocele is significantly higher after surgical ligation than sclero-embolisation, but radiological techniques are associated with higher incidence of post-operative orchiepidydimitys [1754].

Robot-assisted varicocelectomy has a similar success rate compared to the microscopic varicocelectomy technique, although larger prospective randomised studies are needed to establish the most effective method [1755-1757].

Table 38: Recurrence and complication rates associated with treatments for varicocele

Treatment	Recurrence/ Persistence %	Overall complications	Specific Complications
Antegrade sclerotherapy [1757, 1758]	5-9	Hydrocele (5.5%), haematoma, infection, scrotal pain, testicular atrophy, epididymitis	Technical failure 1-9%, left-flank erythema
Retrograde sclerotherapy [1759, 1760]	6-9.8	Hydrocele (3.3%) wound infection, scrotal pain	Technical failure 6-7.5%, adverse reaction to contrast medium, flank pain, persistent thrombophlebitis, venous perforation
Retrograde embolization [1759, 1761]	3-11	Hydrocele (10%) haematoma, wound infection	Technical failure 7-27%, pain due to thrombophlebitis, radiological complications (e.g., reaction to contrast media), misplacement or migration of coils (to femoral vein or right atrium), retroperitoneal haemorrhage, fibrosis, ureteric obstruction, venous perforation
Open operation			
Scrotal operation	-	Testicular atrophy, arterial damage with risk of devascularisation and testicular gangrene, scrotal haematoma, post-operative hydrocele	
Inguinal approach [1762, 1763]	2.6-13	Hydrocele (7.3%), testicular atrophy, epididymo-orchitis, wound complications	Post-operative pain due to incision of external oblique fascia, genitofemoral nerve damage
Open retroperitoneal high ligation [1751, 1764]	15-29	Hydrocele (5-10%), testicular atrophy, scrotal oedema	External spermatic vein ligation failure

Microsurgical inguinal or Subinguinal [1752, 1762, 1765, 1766]	0.4	Hydrocele (0.44%), scrotal haematoma	
Laparoscopy [1724, 1751, 1752, 1767, 1768]	3-6	Hydrocele (7-43%) epididymitis, wound infection, testicular atrophy due to injury of testicular artery, bleeding	External spermatic vein ligation failure, intestinal, vascular and nerve damage; pulmonary embolism; pneumo-scrotum; peritonitis; post-operative pain in right shoulder (due to diaphragmatic stretching during pneumo-peritoneum)

11.4.3.5 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 potential reduction in fertility.	2a
Although the treatment of varicocele in adolescents may be effective, there is a significant risk of over-treatment as the majority of boys with a varicocele will have no fertility problems later in life.	3
Varicocele repair may be effective in men with abnormal semen parameters, a clinical varicocele and otherwise unexplained male factor infertility.	1a
Varicocele repair may improve pregnancy rates and sperm concentration in adult infertile men with abnormal semen analyses, while benefits in sperm motility and normal morphology are less clear.	1a
Although there are no prospective randomised studies evaluating this, meta-analyses have suggested that varicocele repair is associated with sperm appearing in the ejaculate of men with non-obstructive azoospermia.	2
Microscopic approach (inguinal/subinguinal) may have lower recurrence and complications rates than non-microscopic approaches (retroperitoneal and laparoscopic), although no RCTs are available yet.	2a
Varicocele is associated with raised sperm DNA fragmentation (SDF) and intervention has been shown to reduce SDF and may improve the outcomes from ART.	2a

Recommendations	**Strength rating**
In adolescents offer surgery for varicocele associated with a persistent small testis (size difference of > 2 mL or 20%), which should be confirmed on two subsequent visits performed six months apart.	Strong
Do not treat varicocele in infertile men who have normal semen analysis and in men with a sub-clinical varicocele.	Strong
Treat infertile men with a clinical varicocele, abnormal semen parameters and otherwise unexplained infertility in a couple where the female partner has good ovarian reserve to improve fertility rates.	Strong
Varicocelectomy may be considered in men with raised DNA fragmentation with otherwise unexplained infertility or who have suffered from failed of assisted reproductive techniques, including recurrent pregnancy loss, failure of embryogenesis and implantation.	Weak

*11.4.4 **Male accessory gland infections and infertility***

11.4.4.1 Introduction

Infection of the male urogenital tract is a potentially curable cause of male infertility [1769-1771]. The WHO considers urethritis, prostatitis, orchitis and epididymitis to be male accessory gland infections (MAGIs) [1769]. The effect of symptomatic or asymptomatic infections on sperm quality is contradictory [1772]. A systematic review of the relationship between sexually transmitted infections, such as those caused by *Chlamydia trachomatis,* genital mycoplasmas, *Neisseria gonorrhoeae, Trichomonas vaginalis* and viruses, and infertility was unable to draw a strong association between sexually transmitted infections and male infertility due to the limited quality of reported data [1773].

11.4.4.2 Diagnostic evaluation

11.4.4.2.1 Semen analysis

Semen analysis (see Section 11.3.2) clarifies whether the prostate is involved as part of a generalised MAGI and provides information regarding sperm quality.

11.4.4.2.2 Microbiological findings

After exclusion of UTI (including urethritis), > 10^6 peroxidase-positive white blood-cells (WBCs) per millilitre of ejaculate indicate an inflammatory process. Semen culture or polymerase chain reaction (PCR) analysis should be performed for common urinary tract pathogens in all suspected cases of genitourinary tract infections. A concentration of > 10^3 CFU/mL urinary tract pathogens in the ejaculate is indicative of significant bacteriospermia [1774]. The sampling should be delivered the same day to the laboratory because the sampling time can influence the rate of positive micro-organisms in semen and the frequency of isolation of different strains [1775]. The ideal diagnostic test for isolating C. trachomatis in semen has not yet been established [1776], but the most accurate method is PCR [1777-1779].

Historical data show that *Ureaplasma urealyticum* is pathogenic only in high concentrations (> 10^3 CFU/mL ejaculate). Fewer than 10% of samples analysed for *Ureaplasma* exceeded this concentration [1780]. Normal colonisation of the urethra hampers the significance of mycoplasma-associated urogenital infections, using samples such as the ejaculate [1781].

A meta-analysis indicated that Ureaplasma parvum and *Mycoplasma genitalium* were not associated with male infertility, but a significant relationship existed between U. urealyticum (OR: 3.03 95% CI: 1.02–8.99) and *Mycoplasma hominis* (OR: 2.8; 95% CI: 0.93– 3.64) [1782]. For these reasons, the treatment is not always recommended.

The prevalence of human papilloma virus (HPV) in the semen ranges from 2 to 31% in the general population and is higher in men with unexplained infertility (10-35.7%) [1783, 1784]. Systematic reviews have reported an association between male infertility, poorer pregnancy outcomes and semen HPV positivity [1785-1787]. However, data still needs to be prospectively validated to clearly define the clinical impact of HPV infection in semen. Additionally, seminal presence of Herpes Simplex virus (HSV)-2 in infertile men may be associated with lower sperm quality compared to that in HSV-negative infertile men [1772]. However, it is unclear if anti-viral therapy improves fertility rates in these men.

11.4.4.2.3 White blood cells

The clinical significance of an increased concentration of leukocytes in the ejaculate is controversial [1788]. Although leukocytospermia is a sign of inflammation, it is not necessarily associated with bacterial or viral infections, and therefore cannot be considered a reliable indicator [1789]. According to the WHO classification, leukocytospermia is defined as > 10^6 WBCs/mL. Only two studies have analysed alterations of WBCs in the ejaculate of patients with proven prostatitis [1790, 1791]. Both studies found more leukocytes in men with prostatitis compared to those without inflammation (CPPS, type NIH 3b). Furthermore, leukocytospermia should be further confirmed by performing a peroxidase test on the semen. There is currently no evidence that treatment of leukocytospermia alone without evidence of infective organisms improves conception rates [1792].

11.4.4.2.4 Sperm quality

The deleterious effects of chronic prostatitis (CP/CPPS) on sperm density, motility and morphology have been demonstrated in a recent systematic review based on case-controlled studies [1793]. Both *C. trachomatis* and *Ureoplasma spp.* can cause decreased sperm density, motility, altered morphology and increased DNA damage. Data from a retrospective cross-sectional study showed that *U. urealyticum* was the most frequent single pathogen in semen of asymptomatic infertile men; a positive semen culture was both univariably ($p < 0.001$) and multi-variably ($p = 0.04$) associated with lower sperm concentration [1794]. Human papilloma virus is associated with changes in semen density, sperm motility and sperm DNA damage [1783, 1784]. *Mycoplasma spp.* can cause decreased motility and development of antisperm antibodies [1772].

11.4.4.2.5 Seminal plasma alterations

Seminal plasma elastase is a biochemical indicator of polymorphonuclear lymphocyte activity in the ejaculate [1771, 1795, 1796]. 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 through different pathways, but no correlations have been found [1797-1799]. 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 [1800]. However, elevated cytokine levels do not depend on the number of leukocytes in expressed prostatic secretion [1801].

11.4.4.2.6 Glandular secretory dysfunction

The secretory function of the prostate gland can be evaluated by measuring seminal plasma pH, citric acid, or γ-glutamine transpeptidase levels, although these parameters are not evaluated anymore in numerous laboratories; the seminal plasma concentrations of these factors are usually altered during infection and inflammation. However, they are not recommended as diagnostic markers for MAGIs [1802].

11.4.4.2.7 Reactive oxygen species

Reactive oxygen species may be increased in infertile patients with asymptomatic *C. trachomatis* and *M. hominis* infection, with subsequent decrease in ROS upon antibiotic treatment. However, ROS levels in infertile patients with asymptomatic *C. trachomatis* and *M. hominis* in the semen are low, making it difficult to draw any firm conclusions [1803]. Chronic urogenital infections are also associated with increased leukocyte numbers [1804]. However, their biological significance in prostatitis remains unclear [1771].

11.4.4.2.8 Disease management

Only antibiotic therapy of chronic bacterial prostatitis (NIH II according to the classification) has provided symptomatic relief, eradication of micro-organisms, and a decrease in cellular and humoral inflammatory parameters in urogenital secretions. Although antibiotics might improve sperm quality [1805], there is no evidence that treatment of CP/CPPS increases the probability of natural conception [1771, 1806].

Asymptomatic presence of *C. trachomatis* and *M. hominis* in the semen can be correlated with impaired sperm quality, which recovers after antibiotic treatment. However further research is required to confirm these findings [1803].

11.4.4.3 Epididymitis

Inflammation of the epididymis causes unilateral pain and swelling, usually with acute onset. Among sexually active men aged < 35 years, epididymitis is most often caused by *C. trachomatis* or *N. gonorrhoea* [1807, 1808]. Sexually transmitted epididymitis is usually accompanied by urethritis. Non-sexually transmitted epididymitis is associated with UTIs and occurs more often in men aged > 35 years [1809].

11.4.4.3.1 Diagnostic evaluation

11.4.4.3.1.1 Ejaculate analysis

Ejaculate analysis according to WHO Laboratory Manual for the Examination and Processing of Human Semen (6th edn) criteria, may indicate persistent inflammatory activity. Transient reductions in sperm counts and progressive sperm motility can be observed [1807, 1810, 1811]. Semen culture might help to identify pathogenic micro-organisms. Development of stenosis of the epididymal ducts, reduction of sperm count, and azoospermia are more important potential sequelae to consider in the follow-up of bilateral epididymitis (see Section 11.3.2).

11.4.4.3.1.2 Disease management

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 also refer their sexual partners for evaluation and treatment [1812].

11.4.4.4 Summary of evidence and recommendation for male accessory gland infections

Summary of evidence	**LE**
Male accessory gland infections are not clearly associated with impaired natural conception.	3
Antibiotic treatment often only eradicates micro-organisms; it has no positive effect on inflammatory alterations and cannot reverse functional deficits and anatomical abnormalities.	2a

Although antibiotic treatment for MAGIs may result in improvement in sperm quality, it does not enhance the probability of conception.	2a
Data are insufficient to conclude whether antibiotics and antioxidants for the treatment of infertile men with leukocytospermia improve fertility outcomes.	3

Recommendations	Strength rating
Treating male accessory gland infections may improve sperm quality, although it does not necessarily improve the probability of increasing conception.	Weak
Refer sexual partners of patients with accessory sex gland infections that are known or suspected to be caused by sexually transmitted diseases for evaluation and treatment.	Strong

11.5 Non-Invasive Male Infertility Management

11.5.1 ***Empirical treatments***

11.5.1.1 Life-style

Environmental and lifestyle factors may contribute to male infertility acting additively on a susceptible genetic background [81, 1640]. Hence, lifestyle improvement can have a positive effect on sperm parameters.
This includes:

- Weight loss: non-controlled studies have suggested that weight loss can result in improved sperm parameters [81, 1813, 1814]. However, data derived from RCTs are more conflicting. A meta-analysis of 28 cohort studies and 1,022 patients, documented that bariatric surgery did not improve sperm quality and function in morbidly obese men [1815]. Data on ART outcomes are lacking. Furthermore weight loss can improve obesity-related secondary hypogonadism, which may result in better outcomes in couples seeking medical care for infertility [1813, 1815].
- Physical activity: a meta-analysis has documented that moderate-intensity (20–40 metabolic equivalents [METs]/week) or even high-intensity (40–80 METs-h/week) recreational physical activity can result in better semen parameters [1816]. Moreover, physical activity might improve hormonal profile [1813].
- Smoking: data derived from a large meta-analysis of 20 studies with 5,865 participants showed a negative association between smoking and sperm parameters [1817].

Alcohol consumption: Data derived from a recent meta-analysis including 15 cross-sectional studies and 16,395 men suggested that moderate alcohol does not adversely affect semen parameters, whereas high alcohol intake can have a detrimental effect on male fertility [1818] heavy chronic alcohol consumption (defined as > 2 drinks/ day [1819]) can reduce testosterone levels [1819].

11.5.1.2 Antioxidant treatment

Oxidative stress is considered to be of the most important contributing factors in the pathogenesis of idiopathic infertility. Reactive oxygen species, the final products of OS, can impair sperm function acting at several levels, including plasma membrane lipid peroxidation, which can affect sperm motility, the acrosome reaction and chromatin maturation leading to increased SDF [1820]. Accordingly, seminal levels of ROS have been negatively associated with ART outcomes [1821]. Despite this, evidence for the role of antioxidant therapy in male infertility is still conflicting. A Cochrane systematic review and meta-analysis including 34 RCTs and 2,876 couples using various antioxidant compounds, it was concluded that antioxidant therapy had a positive impact on live-birth and pregnancy rates in sub-fertile couples undergoing ART cycles [1822]. Similar results were also reported in a meta-analysis including 61 studies with 6,264 infertile men, aged 18-65 years [1823]. However, the quality of the reported studies is poor. The Males, Antioxidants, and Infertility (MOXI) trial found that antioxidants did not improve semen parameters or DNA integrity compared to placebo among infertile men with male factor infertility. Moreover, cumulative live-birth rate did not differ at 6 months between the antioxidant and placebo groups (15% vs. 24%) [1824]. No clear conclusions were possible regarding the specific antioxidants to use or and/or therapeutic regimes for improving sperm parameters and pregnancy rate [1823].

11.5.1.3 Selective oestrogen receptor modulators

Selective oestrogen receptor modulators (SERMs) block oestrogen receptors at the level of the hypothalamus, which results in stimulation of GnRH secretion, leading to an increase in pituitary gonadotropin release and stimulation of spermatogenesis [1825]. Meta-analysed data derived from eleven RCTs showed that SERMs significantly increased pregnancy rate, sperm and hormonal parameters [1826]. Similar results were confirmed in the latest updated meta-analysis of sixteen studies [1825]. However, previous SR failed to find any association between SERMs and pregnancy rate [1827]. It should be recognised that the quality of the papers considered was low and only a few studies were placebo-controlled. In conclusion, although some positive results relating

to the use of SERMs in men with idiopathic infertility have been reported, no conclusive recommendations can be drawn due to poor quality of the available evidence. Furthermore, complications from the use of SERMs were under-reported.

11.5.1.4 Aromatase inhibitors

Aromatase, a cytochrome p450 enzyme, is present in the testes, prostate, brain, bone, and adipose tissue of men; it converts testosterone and androstenedione to oestradiol and oestrone, respectively. Oestradiol negatively feeds back on the hypothalamus and pituitary to reduce gonadotropic secretions, ultimately affecting spermatogenesis. In this context, aromatase inhibitors (AIs) may decrease oestrogen production by reversibly inhibiting cytochrome p450 isoenzymes 2A6 and 2C19 of the aromatase enzyme complex inhibiting the negative feedback of oestrogen on the hypothalamus resulting in stronger GnRH pulses that stimulate the pituitary to increase production of FSH [1828-1831]. Aromatase activity has been associated with male infertility characterised by testicular dysfunction with low serum testosterone and/or testosterone to oestradiol ratio. In this context, AIs have been reported to increase endogenous testosterone production and improve spermatogenesis in the setting of infertility as an off-label option for treatment [1832]. Either steroidal (testolactone) and non-steroidal (anastrozole and letrozole) AIs significantly improve hormonal and semen parameters in infertile men, with a safe tolerability profile, although prospective RCTs are necessary to better define the efficacy of these medications in this clinical setting [1830, 1832].

*11.5.2 **Summary of evidence and recommendation for Non-Invasive Male Infertility Management***

Summary of evidence	**LE**
In infertile men life style factors including obesity, low physical activity, smoking and high alcohol intake are associated with decreased sperm quality.	2a
In men with idiopathic oligo-astheno-teratozoospermia, life-style changes including weight loss and increased physical activity, smoking cessation and alcohol intake reduction may improve sperm quality and the chances of conception.	2a
No conclusive data are available regarding the beneficial treatment with antioxidants in men with idiopathic infertility, although they may improve semen parameters.	1b
No conclusive data are available regarding the use of selective oestrogen receptor modulators (SERMs) in men with idiopathic infertility.	1b
No conclusive data are available regarding the use of steroidal (testolactone) or nonsteroidal (anastrozole and letrozole) aromatase inhibitors in men with idiopathic infertility.	1b

Recommendations	**Strength rating**
Inform infertile men about the detrimental effects of obesity, low physical activity, smoking and high alcohol intake on sperm quality and testosterone levels. Therefore, advise infertile men to improve life style factors to improve their chances of conception.	Strong
Do not routinely treat patients with idiopathic infertility with antioxidants, selective oestrogen receptor modulators (SERMs) or aromatase inhibitors (Ais).	Weak

*11.5.3 **Hormonal therapy***

11.5.3.1 Secondary hypogonadism

(A brief discussion on Pre-Pubertal-Onset can be found in Appendix 12, online supplementary evidence).

Post-Pubertal Onset: Human Chorionic Gonadotrophin (hCG) alone is usually required first to stimulate spermatogenesis. A starting dose of 250 IU hCG twice weekly is suggested, and if normal testosterone levels are reached, hCG doses may be increased up to 2,000 IU twice weekly. Again, semen analysis should be performed every three months to assess response, unless conception has taken place. If there is a failure of stimulation of spermatogenesis, then FSH can be added (75 IU three times per week, increasing to 150 IU three times per week if indicated). Similarly, combination therapy with FSH and hCG can be administered from the beginning of treatment, promoting better outcomes in men with HH [121]. No difference in outcomes were observed when urinary-derived, highly purified FSH was compared to recombinant FSH [121].

Greater baseline testicular volume is a good prognostic indicator for response to gonadotrophin treatment while previous testosterone therapy can have a negative impact on gonadotropin treatment outcomes in men with hypogonadotropic hypogonadism [1833]. However, this observation has been subsequently refuted by a

meta-analysis that did not confirm a real negative role of testosterone therapy in terms of future fertility in this specific setting [121].

11.5.3.1.1 Secondary hypogonadism due to hyperprolactinemia

In the presence of hyperprolactinaemia, causing suppression of gonadotrophins resulting in sub-fertility the treatment independent of aetiology (including a pituitary adenoma) is dopamine agonist therapy or withdrawal of the drug that causes the condition. Dopamine agonists used include bromocriptine, cabergoline and quinagolide.

11.5.3.2 Primary Hypogonadism

There is no substantial evidence that gonadotrophin therapy has any beneficial effect in the presence of classical testicular failure. Likewise, there are no data to support the use of other hormonal treatments (including SERMs or AIs) in the case of primary hypogonadism to improve spermatogenesis [82, 1834].

11.5.3.3 Idiopathic Male Factor Infertility

There is some evidence that FSH treatment increases sperm parameters in idiopathic oligozoospermic men with FSH levels within the normal range (generally 1.5 – 8 mIU/mL)[1835]. It has also been reported that FSH may improve SDF rates as well as ameliorating AMH and inhibin levels [1836-1839]. High-dose FSH therapy is more effective in achieving a testicular response than lower doses are [1840]. A Cochrane review including six RCTs with 456 participants, different treatment protocols and follow-up periods concluded that FSH treatment resulted in higher live-birth and pregnancy rates compared with placebo or no treatment. However, no significant difference among groups was observed when ICSI or IUI were considered [1841]. In a meta-analysis including 15 trials with > 1,200 patients, similar findings after FSH treatment were observed in terms of both spontaneous pregnancies and pregnancies after ART [1842]. A further study showed that in azoospermic men undergoing TESE-ICSI there were improved SRRs and higher pregnancy and fertilisation rates in men treated with FSH compared to untreated men [1843]. In men with NOA, combination hCG/FSH therapy was shown to increase SRR in only one study [1844]. Human chorionic gonadotrophin alone prior to TESE in NOA has not been found to have any benefit on SRRs [1845]. Overall the evidence for the use of hormone therapy prior to SSR is limited and treatment should be confined to clinical trials and not used routinely in clinical practice.

11.5.3.4 Anabolic Steroid Abuse

Oligospermia or azoospermia as a result of anabolic abuse should be treated initially by withdrawal of the anabolic steroid. There is no common indication for treating this disorder; the management is based on case reports and clinical experience. Usually, adequate sperm numbers and quality will improve over a six to twelve-month period from cessation. If after this interval the condition persists, then hCG without or in combination with FSH as an alternative to clomiphene can be used to stimulate spermatogenesis [1846].

11.5.3.5 Summary of evidence and recommendations for treatment of male infertility with hormonal therapy

Summary of evidence	**LE**
Follicle stimulating hormone (FSH) promotes spermatogenesis and testicular growth during puberty. Human chorionic gonadotropin (hCG) acts like luteinizing hormone (LH) and is used to stimulate intratesticular testosterone production and spermatogenesis in men with hypopituitarism after puberty.	2b
Prepubertal secondary hypogonadism requires the association of FSH and hCG or pulsatile GnRH, even if its use is limited by the difficult administration.	1b
Secondary hypogonadism in adults can be effectively treated with subcutaneous hCG and FSH.	2b
The use of GnRH therapy is more expensive and does not offer any advantages compared to gonadotropins for the treatment of hypogonadotropic hypogonadism.	3
In postpubertal forms of secondary hypogonadism, sequential use of hCG and FSH or their combination from the beginning are options.	1b
Testicular volume is one of the main predictors of response to gonadotropin therapy in men with hypogonadotropic hypogonadism.	2a
Dopamine agonists are used to treat hyperprolactinaemia.	2a
FSH therapy (any formulation) has been associated with improvement in sperm quality and increased spontaneous and assisted pregnancy rates in idiopathic infertile males.	2a
No conclusive recommendations can be given on the use of high-dose FSH in men with idiopathic infertility and prior (m)TESE and therefore cannot be routinely advocated.	2a
Testosterone therapy is contraindicated in infertile men.	1a

Recommendations	Strength rating
Induce spermatogenesis in men with congenital or acquired hypogonadotropic hypogonadism who wish to conceive by effective drug therapy (hCG; human menopausal gonadotropins; recombinant FSH; highly purified FSH).	Strong
Use FSH treatment in men with idiopathic oligozoospermia and FSH values within the normal range, to ameliorate spermatogenesis outcomes.	Weak
Do not treat idiopathic infertility with high dose FSH.	Weak
Do not start hormonal stimulation prior TESE in men with non-obstructive azoospermia (NOA) outside clinical trials.	Weak
Do not use testosterone therapy for the treatment of male infertility.	Strong
Provide testosterone therapy for symptomatic patients with primary and secondary hypogonadism who are not considering parenthood.	Strong
Offer dopamine agonist therapy in men with hyperprolactinemia to improve sperm quality.	Weak
Withdraw anabolic steroids in infertile men for six to twelve months month before considering treatment with selective oestrogen receptor modulators (SERMS) or gonadotrophin therapy to induce spermatogenesis.	Weak

11.6 Invasive Male Infertility Management

*11.6.1 **Obstructive azoospermia***

Obstructive azoospermia (OA) is the absence of spermatozoa in the sediment of a centrifuged sample of ejaculate due to obstruction [1769]. OA occurs in 20-40% of men with azoospermia [1847, 1848] and it is characterised by normal FSH values, testes of normal size and epididymal enlargement [1849]. The most common causes of OA are reported in Table 39.

Table 39: Causes of obstruction of the genitourinary system

Intratesticular (15%)
Epididymis (30-67%)
Infection (acute/chronic epididymitis)
Trauma
Post-surgical iatrogenic obstruction (i.e., MESA, hydrocelectomy or other scrotal surgery)
Congenital epididymal obstruction (usually manifests as congenital bilateral absence of the vas deferens [CBAVD])
Other congenital forms of epididymal obstruction (Young's syndrome)
Vas deferens
Vasectomy
Vasotomy/vasography (with improper technique)
Post-surgical iatrogenic obstruction (i.e., scrotal surgery or herniorraphy)
Congenital unilateral (CUAVD) or bilateral absence of the vas deferens (CBAVD)
Ejaculatory ducts
Cysts (Mullerian utricular, prostatic or seminal vesicular)
Infection (acute/chronic epididymitis)
Traumatic
Postsurgical iatrogenic obstruction
Functional obstruction
Idiopathic/acquired local neurogenic dysfunction

11.6.1.1 Diagnostic evaluation

Clinical history-taking should follow the investigation and diagnostic evaluation of infertile men (See Section 11.3). Risk factors for obstruction include prior surgery, iatrogenic injury during inguinal herniorrhaphy, orchidopexy or hydrocelectomy.

11.6.1.1.1 Clinical examination

Clinical examination should follow the guidelines for the diagnostic evaluation of infertile men. Obstructive azoospermia is indicated by at least one testis with a volume > 15 mL, although a smaller volume may be found in some patients with:

- obstructive azoospermia and concomitant partial testicular failure;
- enlarged and dilated epididymis;
- nodules in the epididymis or vas deferens;
- absence or partial atresia of the vas deferens.

When semen volume is low, or absent a search must be made for spermatozoa in urine after ejaculation. Absence of spermatozoa and immature germ cells in the semen pellet suggest complete seminal duct obstruction.

11.6.1.1.2 Hormone levels

Hormones including FSH and inhibin-B should be normal, but do not exclude other causes of testicular azoospermia (e.g., NOA). Although inhibin-B concentration is a good index of Sertoli cell integrity reflecting closely the state of spermatogenesis, its diagnostic value is no better than that of FSH and its use in clinical practice has not been widely advocated [1850].

11.6.1.1.3 Genetic testing

Cystic fibrose transmembrane conductance regulator gene testing should be performed in any patient with unilateral or bilateral absence of the vas deferens or seminal vesicle agenesis [1851].

11.6.1.1.4 Testicular biopsy

Testis biopsies (including fine needle aspiration [FNA]) without performing simultaneously a therapeutic sperm retrieval are not recommended, as this will require a subsequent invasive procedure. Furthermore, even patients with extremes of spermatogenic failure (e.g., Sertoli Cell Only syndrome [SCOS]) may harbour focal areas of spermatogenesis [1852, 1853].

11.6.1.2 Disease management

11.6.1.2.1 Sperm retrieval

Intratesticular obstruction

Only TESE allows sperm retrieval in these patients and is therefore recommended.

Epididymal obstruction

Microsurgical epididymal sperm aspiration (MESA) or percutaneous epididymal sperm aspiration (PESA) [1854] is indicated in men with CBAVD. Testicular sperm extraction and percutaneous techniques, such as testicular sperm aspiration (TESA), are also options [1855]. The source of sperm used for ICSI in cases of OA and the aetiology of the obstruction do not affect the outcome in terms of fertilisation, pregnancy, or miscarriage rates [1856]. Usually, one MESA procedure provides sufficient material for a number of ICSI cycles [1857] and it produces high pregnancy and fertilisation rates [1858]. Overall, pregnancy outcomes from ICSI in men with OA are comparable between epididymal and testicular sperm and also between fresh and frozen–thawed epididymal sperm [1859]. However, these results are from studies of low evidence [1575].

In patients with OA due to acquired epididymal obstruction and with a female partner with good ovarian reserve, microsurgical epididymovasostomy (EV) is recommended [1860]. Epididymovasostomy can be performed with different techniques such as end-to-site and intussusception [1861]. Anatomical recanalisation following surgery may require 3-18 months. A systematic review indicated that the time to patency in EV varies between 2.8 to 6.6 months. Reports of late failure are heterogeneous and vary between 1 and 50% [1862]. Before microsurgery, and in all cases in which recanalisation is impossible, epididymal spermatozoa should be aspirated intra-operatively by MESA and cryopreserved to be used for subsequent ICSI procedures [1863]. Patency rates range between 65% and 85% and cumulative pregnancy rates between 21% and 44% [1864, 1865]. Recanalisation success rates may be adversely affected by pre-operative and intra-operative findings. Robot-assisted EV has similar success rates but larger studies are needed [1866].

Vas deferens obstruction after vasectomy

Vas deferens obstruction after vasectomy requires microsurgical vasectomy reversal. The mean post-procedural patency and pregnancy rates weighted by sample size were 90-97% and 52-73%, respectively [1864, 1865]. The average time to patency is 1.7-4.3 months and late failures are uncommon (0-12%) [1862]. Robot-assisted vasovasostomy has similar success rates, and larger studies, including cost-benefit analysis, are needed to establish its benefits over standard microsurgical procedures [1866].

The absence of spermatozoa in the intra-operative vas deferens fluid suggests the presence of a secondary epididymal obstruction, especially if the seminal fluid of the proximal vas deferens has a thick "toothpaste" appearance; in this case microsurgical EV may be indicated [1867-1869]. Simultaneous sperm retrieval may be performed for future cryopreservation and use for ICSI; likewise, patients should be counselled appropriately.

Vas deferens obstruction at the inguinal level

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. In these cases, TESE/MESA/PESA or proximal vas deferens sperm aspiration [1870] can be used for cryopreservation for future ICSI.

Ejaculatory duct obstruction

The treatment of ejaculatory duct obstruction (EDO) depends on its aetiology. Transurethral resection of the ejaculatory ducts (TURED) can be used in post-inflammatory obstruction and cystic obstruction [1863, 1871]. Resection may remove part of the verumontanum. In cases of obstruction due to a midline intraprostatic cyst, incision, unroofing or aspiration of the cyst is required [1863, 1871].

Pregnancy rates after TURED are 20-25% [1696, 1871, 1872]. Complications following TURED include epididymitis, UTI, gross haematuria, haematospermia, azoospermia (in cases with partial distal ejaculatory duct obstruction) and urine reflux into the ejaculatory ducts and seminal vesicles [1871].

Alternative therapies for EDO include, seminal vesiculoscopy to remove debris or calculi and balloon dilation and laser incision for calcification on TRUS [1873]. The alternatives to TURED are MESA, PESA, TESE, proximal vas deferens sperm aspiration and seminal vesicle-ultrasonically guided aspiration.

11.6.1.3 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, usually with normal-sized testes and normal reproductive hormones.	3

Recommendations	Strength rating
Perform microsurgical vasovasostomy or epididymovasostomy for azoospermia caused by epididymal or vasal obstruction in men with female partners of good ovarian reserve.	Strong
Use sperm retrieval techniques, such as microsurgical epididymal sperm aspiration (MESA), testicular sperm extraction (TESE) and percutaneous techniques (PESA and TESA) either as an adjunct to reconstructive surgery, or if the condition is not amenable to surgical repair, or when the ovarian reserve of the partner is limited or patient preference is not to undertake a surgical reconstruction and the couple prefer to proceed to ICSI treatment directly.	Strong

11.6.2 ***Non-obstructive azoospermia***

Non-obstructive azoospermia (NOA) is defined as the absence of sperm at the semen analysis after centrifugation, with usually a normal ejaculate volume. This finding should be confirmed at least at two consecutives semen analyses [1558]. The severe deficit in spermatogenesis observed in NOA patients is often a consequence of primary testicular dysfunction or may be related to a dysfunction of the hypothalamus-pituitary-gonadal (HPG) axis.

11.6.2.1 Investigation of non-obstructive azoospermia

Clinical history-taking and clinical examination should follow the investigation and diagnostic evaluation of infertile men (See Section 11.3). Non-obstructive azoospermia can be the first sign of pituitary or germ cell tumours of the testis [1874-1876]. Patients with NOA have been shown to be at increased risk of long-term chronic non-communicable diseases (e.g., cardio-metabolic diseases, cancer) and mortality [1877-1882]. Therefore, investigation of infertile men provides an opportunity for long-term risk stratification for other comorbid conditions [1883]. A complete hormonal investigation and scrotal US are important in the diagnostic work-up of NOA men [1884, 1885].

Concomitant hypogonadism, has been found in about 30% of patients with NOA [288, 1884, 1885]. Biochemical evaluation should be performed to differentiate the types of hypogonadism (i.e., hypogonadotropic hypogonadism vs. hypergonadotropic vs. compensated hypogonadism) as this will determine different therapeutic strategies to treat the hypogonadal male [1886].

Testicular volume is usually low in NOA patients and scrotal US may show signs of testicular dysgenesis (e.g., non-homogeneous testicular architecture and/or microcalcifications) and testicular tumours. Testicular volume may be a predictor of spermatogenic function [1549] and is usually, but not invariably, low in patients with NOA. Some authors have advocated that testicular perfusion detected at US Doppler assessment can predict surgical sperm retrieval at TESE and guide testicular biopsies [1887]; however, to date, data are inconsistent to support a routine role of testicular Doppler evaluation before TESE in order to predict sperm retrieval outcome.

As discussed (see Section 11.3), patients should undergo karyotype analysis [1805, 1806], along with a screening of Y-chromosome micro-deletions [1630, 1888]. In patients with clinical suspicion of CBAVD assessment of mutations in the gene coding for CFTR is also to be recommended [1617, 1618]. Genetic counselling for eventual transmissible and health-relevant genetic conditions should be provided to couples.

11.6.2.2 Surgery for non-obstructive azoospermia

Surgical treatment for NOA is mostly aimed at retrieval of vital sperm directly from the testes (either uni- or bilaterally). This treatment is normally part of ART protocols, including IVF cycles via ICSI. Testicular biopsy before TESE is not recommended.

11.6.2.3 Indications and techniques of sperm retrieval

Spermatogenesis within the testes may be focal, which means that spermatozoa can usually be found in small and isolated foci. With a wide variability among cohorts and techniques, positive SRRs have been reported in up to 50% of patients with NOA [1889, 1890]. Numerous predictive factors for positive SSR have been investigated (see below), although no definitive factors have been demonstrated to predict SSR [1890].

- Histology: The presence of hypospermatogenesis at testicular biopsy showed good accuracy in predicting positive sperm retrieval after TESE compared with maturation arrest pattern or SCOS [1891-1893].
- Hormonal levels: FSH, LH, inhibin B and AMH have been variably correlated with sperm retrieval outcomes, but data from retrospective series are controversial [1582, 1843, 1894-1898].
- Testicular volume has been inconsistently found to be a predictor of positive SSR [1843, 1891, 1897].

In case of complete AZFa and AZFb microdeletions, the likelihood of sperm retrieval is almost zero and therefore TESE procedures are contraindicated [1635]. Conversely, patients with Klinefelter syndrome [1602] and a history of undescended testes have been shown to have higher chance of finding sperm at surgery [1602, 1897, 1899].

Fine needle aspiration mapping

Fine needle aspiration (FNA) mapping technique has been proposed as a prognostic procedure aimed to select patients with NOA for TESE and ICSI [1900]. The retrieved tissue is sent for cytological and histological evaluation to provide information on the presence of mature sperm and on testicular histological pattern. FNA mapping may provide information on the sites with the higher probability of retrieving sperm, thus serving as a guide for further sperm retrieval surgery in the context of ART procedures (e.g., ICSI). A positive FNA requires a secondary therapeutic surgical approach, which may increase the risk of testicular damage, and without appropriate cost-benefit analysis, is not justifiable. No studies have evaluated the salvage rate of mTESE in men who have undergone FNA mapping. Therefore, FNA mapping is not recommended as a primary therapeutic intervention in men with NOA until further RCTs are undertaken.

Testicular sperm aspiration

Testicular sperm aspiration (TESA) is a minimally invasive, office-based, procedure in which testicular tissue is retrieved with a biopsy needle under local anaesthesia. Reported SRRs with TESA range from 11 to 60% according to patient profile and surgical techniques [1901-1904]. Complications after TESA are uncommon and mainly include minor bleeding with scrotal haematoma and post-operative pain [1904]. To date no RCTs have compared SRRs from TESA, cTESE and mTESE. A meta-analysis including data from case-control studies, reported that TESE was two times (95% CI: 1.8-2.2) more likely to result in successful SSR as compared with TESA [1890]. Given the low success rates compared with TESE, TESA is no longer recommended in men with NOA.

Conventional and microTESE

Conventional TESE requires a scrotal incision and open biopsy of the testes [1905]. Reported SRRs in single-arm studies are about 50% [1889]. Observational studies have demonstrated that multiple biopsies yield a higher chance of sperm retrieval [1889, 1906]. Conventional TESE has been associated with a higher rate of complications compared with other techniques [1889]. A total of 51.7% of patients have been found with

intratesticular haematoma at scrotal US 3 months after surgery, with testicular fibrosis observed in up to 30% of patients at six-months' assessment [1907].

Micro TESE is performed with an operative optical microscope to inspect seminiferous tubules at a magnification of 20-25x and it allows to find and extract those tubules which were larger, dilated and opaque as these were more likely to harbour sperm [1905]. The rationale of this technique is to increase the probability of retrieving sperm with a lower amount of tissue sampled and a subsequent lower risk of complications. Lower rates of complications have been observed with mTESE compared to cTESE, both in terms of haematoma and fibrosis [1908]. Both procedures have shown a recovery of baseline testosterone levels after long-term follow-up [1909, 1910]. Therefore, it would be reasonable to provide long-term endocrinological follow-up after TESE (any type) to detect hypogonadism.

A meta-analysis that pooled data analysis of case-control studies comparing cTESE with mTESE showed a lower unadjusted SRR of 35% (95% CI: 30-40) for cTESE and 52% for mTESE [1890]. A meta-analysis comparing cTESE and mTESE in patients with NOA showed a mean SRR of 47% (95% CI: 45;49%). No differences were observed when mTESE was compared with cTESE (46 [range 43-49] % for cTESE vs. 46 [range 42-49] % for mTESE, respectively) [1899]. Meta-regression analysis demonstrated that the SRR per cycle was independent of age and hormonal parameters at enrolment. However, the SRR increased as a function of testicular volume. Retrieved sperms resulted in a live-birth rate of up to 28% per ICSI cycle [1912]. The difference in surgical sperm retrieval outcomes between the two meta-analyses may be explained by the data studied [1890] only one analysed case control studies whilst Corona *et al.*, [1912] also included the single randomised controlled trial), but it is important to note that all the studies comparing cTESE and mTESE have shown that the latter is superior in retrieving sperm.

In this context, studies showed a higher chance of sperm retrieval with mTESE only for patients with a histological diagnosis of SCOS [1908]. In such cases, results ranged from 22.5 to 41% and from 6.3 to 29% for mTESE vs. cTESE, respectively [1908]. Conversely, no difference between the two techniques has been found when comparing patients with a histology suggestive of maturation arrest [1908]. A single study showed a small advantage of mTESE when hypospermatogenesis was found [1910].

In a study assessing the role of salvage mTESE after a previously failed cTESE or TESA, sperm were successfully retrieved in 46.5% of cases [1857]. In studies reporting SSR by micro-TESE for men who had failed percutaneous testicular sperm aspiration or non-microsurgical testicular sperm extraction, the SRR was 39.1% (range 18.4-57.1%) [1911, 1912]. Similarly, a variable SRR has been reported for salvage mTESE after a previously failed mTESE (ranging from 18.4% to 42.8%) [1913, 1914].

A recent meta-analysis investigated the risk of hypogonadism after TESE due to testicular atrophy [1915]; patients with NOA experienced a mean 2.7 nmol/L decrease in total testosterone 6 months after cTESE, which recovered to baseline within 18-26 months. Lower rates of complications have been observed with mTESE compared to cTESE, both in terms of haematoma and fibrosis [1908]. Both procedures have shown a recovery of baseline testosterone levels after long-term follow-up [1909, 1910].

The main limitation to contemporary literature is the paucity of randomised controlled studies comparing cTESE and mTESE. Although no difference in SSR was observed between cTESE/mTESE techniques in patients with NOA in the latest and most comprehensive meta-analysis [1899], it is important to note that in all the individual trials comparing cTESE and mTESE the latter was superior in retrieving sperm. Furthermore, the current data suggests that mTESE has less complications than cTESE and therefore the consensus opinion of the guidelines panel is that mTESE is the optimum approach for surgical sperm retrieval procedures. However, this is based on low-quality evidence and larger RCTs comparing SSR, risks and costs between the two techniques are urgently needed.

Hormonal therapy prior to surgical sperm retrieval approaches

Stimulating spermatogenesis by optimising intratesticular testosterone (ITT) has been proposed to increase the chance of SSR in men with NOA. Similarly, increasing FSH serum levels could stimulate spermatogenesis. To this aim, several treatment options are available, thus including hCG and/or FSH [1838, 1916, 1917] or SERMs [1918], but a standardized protocol is lacking.

No RCT has shown a benefit of hormonal treatment to enhance the chances of sperm retrieval among patients with idiopathic NOA [1919]. A meta-analysis has suggested that hormone stimulation prior to TESE might improve SRR in eugonadal but not in hypergonadotropic hypogonadal patients [1920]; however, the included studies had moderate or severe risk of bias and randomised studies are needed to confirm these findings.

Hormonal therapy has also been proposed to increase the chance of sperm retrieval at salvage surgery after previously failed cTESE or mTESE. . Only small retrospective studies with conflicting results have been conducted [1838, 1920-1922]. The histological finding of hypo-spermatogenesis emerged as a predictor of sperm retrieval at salvage surgery after hormonal treatment [1922]. Patients should be counselled that the evidence for the role of hormone stimulation prior to sperm retrieval surgery in men with idiopathic NOA is limited [1923]. Currently, it is not recommended in routine practice.

11.6.2.4 Recommendations for Non-Obstructive Azoospermia

Summary of evidence	**LE**
Patients with NOA are at increased risk of long term cardio-metabolic diseases, cancer and mortality.	3
Hypogonadism is present in about one third of men with non-obstructive azoospermia (NOA), before surgical for sperm retrieval.	3
Surgery for sperm retrieval is mandatory in NOA men before ART.	1b
Fine needle aspiration (FNA) and testicular sperm aspiration (TESA) have lower sperm retrieval rates compared to TESE in patients with NOA.	1b
FNA requires a secondary therapeutic surgical approach, which may increase the risk of testicular damage, and without appropriate cost-benefit analysis it is not justifiable.	2a
No definitive predictors of positive sperm retrieval before TESE have been identified.	1b
Microdissection TESE has been associated with higher rates of sperm retrieval and lower complications than conventional TESE.	2a
No conclusive data are available regarding the benefit of use of medical therapy before TESE (e.g., recombinant follicle-stimulating hormone [rFSH]; highly purified FSH; human chorionic gonadotrophin; aromatase inhibitors or selective oestrogen receptor modulators [SERMs]) in patients with NOA.	2a

Recommendations	**Strength rating**
Confirm a diagnosis of non-obstructive azoospermia (NOA) in two consecutive semen analyses, when no sperm are found after centrifugation.	Strong
Perform a comprehensive assessment, including detailed medical history, hormonal profile, genetic tests and scrotal ultrasound to investigate the underlying aetiology and associated co-morbidity in patients with NOA.	Strong
Genetic counselling is mandatory in couples with genetic abnormalities prior to any assisted reproductive technology.	Strong
Perform surgery for sperm retrieval in men who are candidates for assisted reproductive technology (i.e., ICSI).	Strong
Do not perform surgery for sperm retrieval in patients with complete AZFa and AZFb microdeletions, since the chance of sperm retrieval is zero.	Strong
Do not perform fine needle aspiration mapping (FNA) and testicular sperm aspiration (TESA) in patients with NOA.	Strong
Do not perform FNA mapping as a prognostic procedure prior to definitive testicular sperm extraction (any type) in patients with NOA in routine clinical practice.	Weak
Use microdissection TESE as the treatment of choice to retrieve sperm in patients with NOA.	Weak
Do not consider pre-operative biochemical and clinical variables as sufficient and reliable predictors of sperm retrieval outcome at surgery in patients with NOA.	Weak
Do not routinely use medical therapy, e.g. hormonal stimulation iin men with NOA and hypergonadotrophic hypogonadism before TESE (any type) to improve sperm recovery.	Weak

11.7 Assisted Reproductive Technologies

Assisted reproductive technology consists of procedures that involve the *in vitro* handling of both human oocytes and sperm, or of embryos, with the objective of establishing pregnancy. A limited summary of ARTs including a discussion on safety can be found in Appendix 13 online supplementary evidence.

11.8 Psychosocial aspects in men's infertility

Male infertility impacts men's psychological well-being resulting in emotional distress and challenges men's sense of identity. Is worth noting that a failed treatment often results in a prolonged grief response, requiring post-treatment psychological support [1924]. The mental health expert is thus regarded as part of the infertility intervention team, acting in all intervention stages, using strategies that may range from psycho-education techniques to more comprehensive psycho-therapeutic approaches [1925]. Furthermore, there should be a deeper focus on preventive policies; It has been recognised that men, such as women, want to become parents. Yet, they have very limited knowledge on infertility related risk factors, including a lack of awareness on the age-related decline in fertility, and tend to overestimate the chance of spontaneous conception [1926, 1927].

12. LATE EFFECTS, SURVIVORSHIP AND MEN'S HEALTH

The EAU Guidelines Panel of Sexual and Reproductive Health have extensively reviewed the literature to provide guidance on: (i) late effects of urological diseases (both occurring during childhood and adulthood) on male sexual and reproductive health; (ii) late and long-term effects of cancers on male sexual and reproductive health; and, (iii) future directions to support personalised medicine strategies for promotion and raising the awareness of male sexual and reproductive health overall.

A systematic literature search for original English-language publications and review articles published up to December 2019 and a further search up to December 2020 were performed using both Pubmed and Google, yielding only a limited number of papers addressing the role of health care professionals in supporting male patients who have suffered from cancers in terms of sexual and reproductive health, or the concept of Men's Health programmes.

Despite considerable public health initiatives over the past few decades, the Panel has observed that there is still a significant gender gap between male and female in life expectancy [1928]. The main contributors to male mortality in Europe are non-communicable diseases (namely CVDs), cancer, diabetes and respiratory disease) and injuries [1679], as highlighted in a recent WHO report disproving the prevailing misconception that the higher rate of premature mortality among men is a natural phenomenon [1928, 1929]. The recent pandemic situation linked with SARS-CoV-2 infection associated diseased (COVID-19) further demonstrates how the development of strategies dedicated to male health is of fundamental importance [1930].

The WHO report also addresses male sexual and reproductive health which is considered under-reported, linking in particular male infertility, as a proxy for overall health, to serious diseases in men [1878, 1879, 1931-1934]. These data suggest that health care policies should redirect their focus to preventive strategies and in particular pay attention to follow-up of men with sexual and reproductive complaints [1881, 1935]. [1935]. Considering that infertile men seem to be at greater risk of death, simply because of their inability to become fathers, is unacceptable [1882]. The Panel aims to develop a concept of a more streamlined and holistic approach to men's health.

For these guidelines, the Panel aimed to challenge clinicians to look beyond the pathology of disorders alone and consider the potential associations with other health disorders. Men with varicoceles have a higher incidence of heart disease and higher risk of diabetes and hyperlipidaemia following diagnosis [1935]. A diagnosis of infertility may have a profound psychological impact on men (and their partners), potentially resulting in anxiety, enduring sadness, anger, and a sense of personal inadequacy and "unmet masculinity" [1936]. A combination of factors, personality, sociocultural background, and specific treatments/professional support, will determine how men cope with this diagnosis [1925].

The most common cancer among European men (excluding non-melanoma skin cancer) is PCa [1937]. Due to new therapeutic approaches, survival rates have improved significantly [1938] and as men live longer, health-

related quality of life and related sexual well-being will become increasingly important [288]. Regardless of the type of treatment used [1692], sexual dysfunction and distress are common post-treatment complications [289, 1939-1941].

Furthermore, little is known about the relevance of fertility and fertility-preservation strategies in cancer survivors [1942-1946]. In PCa, it has been documented that the psychological consequences persist, even after complete remission or cure and erectile function is restored [1947]. In addition, special attention must be given to gay and bisexual men with PCa; these men present specific sexual concerns steaming from heteronormativity standards that have a negative impact in health care quality [1948]. Therefore urologists dealing with sexual and reproductive health are primed to act as a vanguard for cancer survivorship programmes.

Finally, the relationship between ED and heart disease has been firmly established for well over two decades [1949-1955]. Cadiovascular disease is the leading cause of both male mortality and premature mortality [1956-1959]. Studies indicate that all major risk factors for CVD, including hypertension, smoking and elevated cholesterol are more prevalent in men than women [1960-1966]. Given that ED is an established early sign of atherosclerotic disease and predicts cardiovascular events as an independent factor [1951], it provides urologists with the unique opportunity for CVD screening and health modification and optimise CVD risk factors, while treating men's primary complaint (e.g., ED). Currently, both the EAU and AUA guidelines recommend screening for CVD risk factors in men with ED and late onset hypogonadism [1967-1969] (see Sections 3.5.5 and 5.2).

There is clearly a need to prospectively collect data addressing all aspects of male health, including CVD screening protocols and assess the impact of primary and secondary preventive strategies. The EAU Sexual and Reproductive Health Guidelines Panel aims to promote and develop a long-term strategy to raise men's health at a global level.

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14. CONFLICT OF INTEREST

All members of the EAU Sexual and Reproductive Health Guidelines 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 publicly 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.

15. CITATION INFORMATION

The format in which to cite the EAU Guidelines will vary depending on the style guide of the journal in which the citation appears. Accordingly, the number of authors or whether, for instance, to include the publisher, location, or an ISBN number may vary.

The compilation of the complete Guidelines should be referenced as:
EAU Guidelines. Edn. presented at the EAU Annual Congress, Paris 2024. ISBN 978-94-92671-23-3.

If a publisher and/or location is required, include:
EAU Guidelines Office, Arnhem, The Netherlands. http://uroweb.org/guidelines/compilations-of-all-guidelines/

References to individual guidelines should be structured in the following way:
Contributors' names. Title of resource. Publication type. ISBN. Publisher and publisher location, year.

EAU Guidelines on

Paediatric Urology

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European Association of Urology

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1. INTRODUCTION

1.1 Aim

The European Association of Urology (EAU) Paediatric Urology Guidelines Panel has prepared these Guidelines with the aim of increasing the quality of care for children with urological conditions. This Guideline document is limited to a number of common clinical pathologies in paediatric urological practice, as covering the entire field of paediatric urology in a single guideline document is unattainable.

The majority of urological clinical problems in children are specialised 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 team is available.

Over time, paediatric urology has 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 caregivers into account. Guidelines are not mandates and do not purport to be a legal standard of care.

1.2 Panel composition

The EAU 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: http://uroweb.org/guideline/paediatric-urology/.

1.3 Available publications

A quick reference document (Pocket guidelines) is available this is an abridged versions which may require consultation together with the full text version. A number of translated versions, alongside several scientific publications are also available [1-7]. 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 [8]. This 2024 publication includes a number of updated chapters and sections as detailed below.

1.5 Summary of changes

The literature for the complete document has been assessed and updated, wherever relevant. Key changes in the 2024 publication:

- Section 3.4 Fertility preservation in children and adolescents (new section)
- Section 3.5 Hydrocele
- Section 3.19 Congenital lower urinary tract obstruction
- Section 3.21 Emergencies in Paediatric Urology (new section)
- Section 3.22 Paediatric urological trauma
- Section 3.23 Peri-operative fluid management
- Section 3.24 Basic principles of laparoscopic surgery in children

2. METHODS

2.1 Introduction

These Guidelines were compiled based on current literature following a structured review. Databases covered by the searches included Pubmed, Ovid, EMBASE and the Cochrane Central Register of Controlled Trials and the Cochrane Database of Systematic Reviews. Application of a structured analysis of the literature was not possible in many conditions due to a lack of well-designed studies. The limited availability of large randomised controlled trials (RCTs) - influenced also by the fact that a considerable number of treatment options relate to surgical interventions on a large spectrum of different congenital problems - means this document is largely a consensus document. Clearly there is a need for continuous re-evaluation of the information presented in this document.

Recommendation within the Guidelines are developed by the panels to prioritise clinically important care decisions. The strength of each recommendation is determined by the balance between desirable and undesirable consequences of alternative management strategies, the quality of the evidence (including certainty of estimates), and the nature and variability of patient values and preferences. This decision process, which can be reviewed in the strength rating forms which accompany each guideline statement, addresses a number of key elements:

1. the overall quality of the evidence which exists for the recommendation [9];
2. the magnitude of the effect (individual or combined effects);
3. the certainty of the results (precision, consistency, heterogeneity and other statistical or study related factors);
4. the balance between desirable and undesirable outcomes;
5. the impact and certainty of patient values and preferences on the intervention

Strong recommendations typically indicate a high degree of evidence quality and / or a favourable balance of benefit to harm and patient preference. Weak recommendations typically indicate availability of lower quality evidence, and/or equivocal balance between benefit and harm, and uncertainty or variability of patient preference [10].

Additional information can be found in the general Methodology section 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 Peer review

All chapters of the Paediatric Urology Guidelines were peer-reviewed in 2015.

3. THE GUIDELINE

3.1 Phimosis and other abnormalities of the penile skin

The prepuce or foreskin of the penis is often a cause of concern to parents of young boys and physicians alike [11] with 10% seeking medical advice [12]. While there are some pathological abnormalities of the foreskin, these are in fact quite rare and must be discerned from physiological variations or developmental stages. In this chapter we highlight normal development, it's variations and how to discern this from abnormal foreskin requiring treatment, as well as various treatment options.

3.1.1 Terminology, epidemiology and pathophysiology

At birth the foreskin can be retracted in 4% of boys. In 42% of neonates the tip of the glans cannot be visualised. By the end of the first year of life, retraction of the foreskin behind the glandular corona is possible in approximately 50% of boys; this increases to 89% by the age of three years. Non-retractability of the foreskin can be a physiological phase which does not require treatment in the absence of symptoms, such as painful erections or balanitis.

Phimosis

In phimosis the inability to retract the foreskin over the glans penis is due to a narrow ring in the prepuce. Several factors have been suggested to aid in the gradual dilation of this ring: histological changes in the prepuce, hormonal factors and stretching due to erections. While erections occur even antenatally, these may be insufficient to stretch the foreskin if it is relatively long, and therefore relative phimosis can be present for a prolonged period [13].

Epidemiological studies of the natural course of phimosis are difficult, as they are affected by treatment of a subgroup of subjects. Nonetheless, the incidence of phimosis is 9-20% in five to thirteen year-olds and just 1% in males aged sixteen to eighteen years [13, 14].

Preputial adhesions

Another cause of non-retractability of the prepuce are adhesions of the foreskin to the glans, and this must be distinguished from phimosis. Usually when adhesions are present, partial retraction is possible and the meatus can be visualised [14]. Adhesions are a physiological phenomenon of variable duration, present in 63% of 6-7 year-olds and 3% of 16-17 year-olds without phimosis [14]. Progressive separation of the inner prepuce from the glans is associated with build-up of epithelial debris (smegma) and aided by penile erections. During this process smegma can accumulate into nodules that may be mistaken for cysts. When released from between the skin layers smegma can resemble purulent discharge, especially when mixed with urine. There may temporarily be focal erythema. In the absence of other signs of infection, this should not be confused with balanitis.

Once adhesions between the glans and inner prepuce are resolved there may be ballooning of the foreskin during voiding, particularly if the opening of the prepuce is still relatively narrow. Ballooning is not a sign of obstructed voiding and uroflows have been shown to be normal with ballooning [15]. Therefore, ballooning may be a physiological phase, and it should only be considered a problem in case of (recurring) balanitis.

Paraphimosis

In paraphimosis the foreskin has been retracted and cannot be brought back down to cover the glans of the penis. In children it is most likely due to manipulation, with an incidence reported to be as low as 0,2% [12]. The risk of paraphimosis is higher if there is relative phimosis. The narrow ring in the retracted prepuce may constrict the shaft at the level of the sulcus, leading to edema of the glans and retracted foreskin. Impaired perfusion may lead to necrosis of the prepuce and ultimately of the glans. Paraphimosis must be regarded as a medical emergency requiring urgent treatment [16].

Balanitis/balanoposthitis

Balanoposthitis may be defined as erythema and swelling of the glans (balanitis) and/or foreskin (posthitis), with discharge of pus. It should not be confused with focal irritation due to retention of droplets of urine under the foreskin. Balanoposthitis may be seen in 6% of uncircumcised boys [12, 17].

Balanitis xerotica obliterans

Balanitis xerotica obliterans (BXO) is a non-painful chronic inflammatory disease which may affect the glans, foreskin, meatus and urethra. As such it is a genital form of lichen sclerosus et atrophicus [13]. Balanitis xerotica obliterans may lead to scarring, phimosis and urethral outflow problems. Histological analysis of the prepuces of children and adolescents undergoing circumcision for medical reasons shows signs of BXO in 35%-53% [18]; in boys younger than ten years this is 17% [19, 20].

Inconspicuous penis

There are several types of concealed or inconspicuous penis, which should be differentiated from truly small penis such as micropenis with abnormal size of the corporeal bodies or even aphallia.

- Buried penis and megaprepuce are congenital anomalies in which the skin is folded abnormally around the shaft. The opening of the prepuce can be narrow, prohibiting retraction similar to regular phimosis, but may also be normal. Occasionally buried penis may be due to abnormal prepubic fat distribution, which may be self-limiting with growth or weight loss.
- In webbed penis the penoscrotal angle is abnormal due to the scrotum being attached high on the ventral side of the shaft.
- Trapped penis is an iatrogenic form of buried penis which may be caused by resection of too much skin during circumcision [21].

*3.1.2 **Classification and diagnostic evaluation***

In order to determine which cases require treatment, phimosis should be divided into a physiological and pathological type. Physiological phimosis is most likely to resolve over time without intervention, whereas pathological phimosis may not.

In physiological phimosis there is no sign of scarring, and upon retraction the inner prepuce is seen bulging outward from the narrow ring in the prepuce ("pouting"). In pathological or secondary phimosis there is scarring, the narrow ring in the prepuce is fibrous, often white and thickened, and the inner layer of the prepuce is not seen coming out [22]. Balanitis xerotica obliterans is a special form of pathological phimosis.

The diagnosis of adhesions, phimosis and paraphimosis is made by physical examination alone, and this can differentiate between physiological variations or pathological abnormalities. If the prepuce is not retractable, or only partly retractable, and shows a constrictive ring upon retraction 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, the inner prepuce may be adherend to the glans and/or frenulum breve.

Balanitis xerotica obliterans remains a histopathological diagnosis as clinically discerning BXO from simple pathological phimosis by may be difficult, particularly to the untrained eye. Histopathological examination of resected foreskin is warranted due to the consequences of this diagnosis with regards to follow-up [23, 24].

In buried penis, the shaft itself appears shorter upon inspection but is of normal size upon palpation, hence the name. In megaprepuce the shaft may have a normal appearance or it may resemble buried penis. The diagnosis is made based on the aspect of the penis during voiding. When the enlarged space between shaft and inner prepuce fills up with urine during voiding, this causes the entire penis to swell. Megaprepuce can be discerned from regular phimosis, in which only the tip of the penis may demonstrate ballooning. It may be helpful if caregivers show a photo or even video of the aspect of the penis during voiding.

*3.1.3 **Management***

Hygiene

The foreskin should not be retracted for cleaning until this can be done easily. It should be stressed to parents/caregivers that forced retraction of a narrow foreskin may cause scar formation resulting in secondary pathological phimosis [25]. Care should be taken to reduce the foreskin back down over the glans to prevent paraphimosis. Once the foreskin is retractable this may be regularly done during bathing and becomes necessary for hygienic reasons from puberty. The production of smegma appears to increase at puberty, coinciding with the age at which most boys can retract their foreskin [22].

Conservative / medical management

Physiological phimosis and adhesions do not need treatment, unless there are accompanying urogenital abnormalities. Conservative medical treatment is a valid option for primary pathological phimosis. Class 4 corticosteroid therapies were more effective over placebo and manual stretching [26]. Topical corticoid (0.05-0.1%) can be administered twice a day over a period of 4-8 weeks with a success rate of > 80% [26-29]. A publication showed that lower class corticosteroids may be almost equally effective [30]. A recurrence rate of up to 17% can be expected [31]. Effectivity of topical corticosteroids is likely to be influenced by correct application, which must be directly onto the narrow ring under gentle retraction. Similarly, after finishing the corticosteroid treatment recurrence should be prevented by continuing daily retraction of the prepuce [32]. While all types of phimosis may respond to corticosteroid treatment, the success rate may be lower in pathological phimosis. If BXO is suspected, consultation with a dermatologist should be considered [33].

Corticosteroid treatment has no systemic side effects and mean blood cortisol levels are not significantly different from an untreated group of patients [34]. The hypothalamic pituitary-adrenal axis was not influenced by local corticoid treatment [35]. However, if treatment is continued for too long or too much product is used this may cause focal atrophy and vulnerability of the skin. In general, cream may be associated with dryness and irritation, due to the nature of the product compared to ointment. Adhesion of the foreskin to the glans does not respond to corticosteroid treatment [27].

Operative management

Circumcision for non-medical reasons, such as routine circumcision for cultural, religious or hygienic considerations, is not discussed in this chapter.

Medical indications for surgical intervention for phimosis are recurrent balanoposthitis or symptomatic therapy-resistant phimosis. Simple ballooning of the foreskin during micturition is not an indication for surgery per se. Several indications for circumcision in the absence of symptomatic phimosis have been proposed. In boys with increased risk of urinary tract infections (UTIs) due to congenital upper tract

abnormalities, circumcision may be performed to reduce the risk of UTIs [36-39]. Male circumcision significantly reduces the bacterial colonisation of the glans penis with regard to both non-uropathogenic and uropathogenic bacteria [40]. However, resolution of phimosis by corticosteroid treatment may have similar results as it was also associated with substantial reduction in recurrent UTI in uncircumcised infants [41]. (See Chapter 3.10 on urinary tract infections in children and Chapter 3.15 on vesicoureteric reflux).

Routine neonatal circumcision to prevent penile carcinoma is not indicated. A meta-analysis could not find any risk in uncircumcised patients without a history of phimosis [42].

The type of operative treatment of phimosis in children is dependent on the caregivers' preferences and can be preputioplasty or circumcision. In preputioplasty the objective is to preserve the prepuce while achieving a wider foreskin circumference with full retractability. Several surgical techniques have been described to achieve this goal: dorsal incision, partial circumcision, trident preputial plasty, combining two Z-plasties and Y-plasty [43, 44]. The main disadvantage of preputioplasty is the inherent potential for recurrence of phimosis [45].

In circumcision, the prepuce is resected completely. Contra-indications for circumcision are: an acute local infection and congenital anomalies of the penis, particularly hypospadias, buried penis and megaprepuce, epispadias and congenital penile curvature, as the foreskin may be required for a reconstructive procedure [46, 47].

When surgically correcting phimosis, additional issues should be addressed during the same session: adhesions are released, an associated frenulum breve is corrected by frenulotomy and the meatus is calibrated with meatoplasty added if necessary.

Paraphimosis treatment

Treatment of paraphimosis consists of manual compression of the oedematous tissue with a subsequent attempt to retract the tightened foreskin over the glans penis [48, 49]. If this maneuver fails, a dorsal incision of the constrictive ring is required. Following acute redressing of the foreskin, additional treatment is recommended to correct any anomalies which increase the chance of recurrence. Patients should be counselled regarding prevention of paraphimosis by correctly redressing their foreskin after retraction.

*3.1.4 **Complications***

Complications following circumcision vary and have been reported between 0-30% [50]. Hung *et al.* found 2.9% complications in non-neonates during a 5-year follow-up period; 2.2% were early (within 30 days after circumcision). Non-healing wounds, haemorrhage, wound infection, meatal stenosis, redundant skin, non-satisfying cosmetic appearance and trapped penis all may occur [51]. The incidence of post-circumcision meatal stenosis is higher in boys with confirmed BXO compared to those who underwent circumcision for phimosis without BXO (20% vs 6%) [23]. Overall, the risk of complications appears low when done by professionals in a medical setting.

*3.1.5 **Follow-up***

Any preputial surgery requires early follow-up of four to six weeks after surgery. In case of BXO, prolonged follow up is warranted and may involve a dermatologist. Balanitis xerotica obliterans is associated with meatal pathology (stenosis) after circumcision in up to 20% of boys [20, 52, 53].

*3.1.6 **Summary of evidence and recommendations for the management of phimosis***

Summary of evidence	**LE**
Non-retractability of the foreskin, preputial adhesions and ballooning may be a physiological phase before puberty and do not require treatment in the absence of symptoms.	3
Forced retraction of a narrow foreskin should be avoided to prevent scar formation which may result in secondary pathological phimosis.	3
Conservative treatment of phimosis with topical corticosteroids (ointment or cream) has a high success rate, but surgical treatment may be considered if preferred by caregivers or patients.	1b
Balanitis xerotica obliterans warrants prolonged follow up due to risk of meatal stenosis or urethral involvement.	2

Recommendations	Strength rating
Offer topical corticosteroids (ointment or cream) as first-line treatment in symptomatic phimosis.	Strong
Consider surgical intervention if patient/caregivers prefer for symptomatic phimosis.	Strong
Offer circumcision in case of Balanitis xerotica obliterans (BXO) or phimosis refractory to treatment.	Strong
Offer treatment for asymptomatic phimosis in infants with a risk of recurrent urinary tract infection due to upper urinary tract abnormalities (vesicoureteral reflux or posterior urethral valves).	Strong
Inform patients about the risk of meatal stenosis in BXO.	Strong
Await spontaneous resolution of asymptomatic preputial adhesions before puberty.	Weak
Treat paraphimosis by manual reposition and proceed to surgery if this fails.	Strong
Do not perform simple circumcision if phimosis is associated with other penile anomalies such as buried penis, congenital penile curvature, epispadias or hypospadias.	Strong

3.2 Management of undescended testes

*3.2.1 **Background***

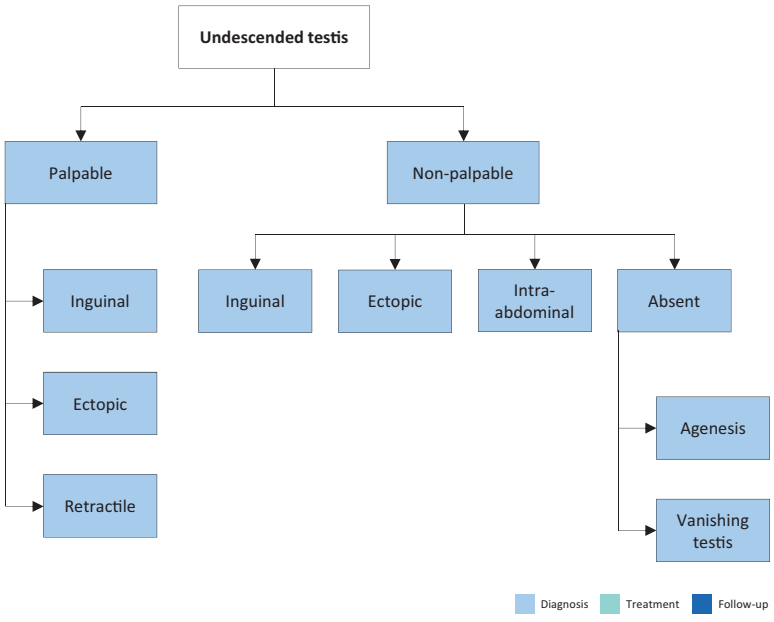
Cryptorchidism or undescended testis is one of the most common congenital malformations of male neonates. Incidence varies and depends on gestational age, affecting 1.0-4.6% of full-term and 1.1-45% of preterm neonates. Following spontaneous descent within the first months of life, nearly 1.0% of all full-term male infants still have undescended testes at one year of age [54]. This congenital malformation may affect both sides in up to 30% of cases [55]. 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 [56].

*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 [57]. Acquired undescended testes can be caused by entrapment after herniorrhaphy or spontaneously referred to as ascending testis.

Palpable testes include true undescended testes and ectopic testes. Non-palpable testes include intra-abdominal, inguinal, absent, and sometimes also some ectopic testes. Most importantly, the diagnosis of palpable or non-palpable testis needs to be confirmed once the child is under general anaesthesia, as this is the first step of any surgical procedure for undescended testes.

Figure 1: Classification of undescended testes



3.2.2.1 Palpable testes

Undescended testes

A true undescended testis is on its normal path of descent but is halted on its way down to the scrotum. Depending on the location, the testes may be palpable or not, as in the case of testes arrested in the inguinal canal.

Ectopic testes

If the position of a testis is outside its normal path of descent and outside the scrotum, the testis is considered to be ectopic. The most common aberrant position is in the superficial inguinal pouch. Sometimes an ectopic testis can be identified in a femoral, perineal, pubic, penile or even contralateral position. Usually, there is no possibility for an ectopic testis to descend spontaneously to the correct position; therefore, it requires surgical intervention. In addition, an ectopic testis might not be palpable due to its position.

Retractile testes

Retractile testes have completed their descent into a proper scrotal position but can be found again in a suprascrotal position along the path of their normal descent. This is due to an overactive cremasteric reflex [58]. 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 [59].

3.2.2.2 Non-palpable testes

Among the 20% of non-palpable testes, 50-60% are intra-abdominal, canalicular or peeping (right inside the internal inguinal ring). The remaining 20% are absent and 30% are atrophic or rudimentary.

Intra-abdominal testes

Intra-abdominal testes can be located in different positions, with most of them being found close to the internal inguinal ring. However, possible locations include the kidney, anterior abdominal wall, and retrovesical space. In the case of an open internal inguinal ring, the testis may be peeping into the inguinal canal.

Absent testes

Monorchidism can be identified in up to 4% of boys with undescended testes, and anorchidism (bilateral absence) in < 1%. Possible pathogenic mechanisms include testicular agenesis and atrophy after intrauterine torsion with the latter one most probably due to an *in utero* infarction of a normal testis by gonadal vessel torsion. The term “vanishing testis” is commonly used for this condition [60].

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

Caregivers 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 [61]. 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 [62]. 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 the event 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 [63]. Nevertheless, this does not preclude surgical exploration since the sign of compensatory hypertrophy is not specific enough [64, 65].

In the event 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 [66].

3.2.3.3 Imaging studies

Imaging studies cannot determine with certainty that a testis is present or not [67]. Ultrasound (US) lacks the diagnostic sensitivity to detect the testis confidently or establish the absence of an intra-abdominal testis [68]. Consequently, the use of different imaging modalities, such as US or Magnetic resonance imaging (MRI) [69], 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) [68].

3.2.4 ***Management***

Treatment should be started at the age of six months. After that age, undescended testes rarely descend [70].
Any kind of treatment leading to a scrotally positioned testis should be finished by twelve months, or eighteen months at the latest, because histological examination of undescended testes at that age has already revealed a progressive loss of germ cells and Leydig cells [71]. 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 [72].

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 [73, 74].

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 limited success rate of only 20% [75]. However, it must be taken into account that almost 20% of these descended testes have the risk of re-ascending later [76]. 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 [73]. Some authors recommend combined hCG-GnRH treatment. Unfortunately, it is poorly documented and the treatment groups were diverse. Some studies reported successful descent in up to 38% of non-responders to monotherapy [77]. The Panel consensus is that endocrine treatment to achieve testicular descent is not recommended (LE: 4).

Human chorionic gonadotropin

Human chorionic gonadotropin (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 fourteen days [78]. Similar response rates were achieved with 500 IU once weekly and 1.50 IU three times weekly [79]. 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 [80].

Gonadotropin-releasing hormone

Gonadotropin-releasing hormone (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 per day in three divided doses, for four weeks. Success rates are wide ranging, from 9 to 60%, due to multiple treatment strategies and heterogeneous patient populations [81].

3.2.4.1.2 Medical therapy for fertility potential

Hormonal treatment may improve fertility indices [81, 82] 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 [83]. 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 [81].

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 [84].

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 [85]. The consensus of the Panel is to recommend endocrine treatment with GnRH analogues in a dosage described above for boys with bilateral undescended testes to preserve the fertility potential (LE: 4).

3.2.4.2 Surgical therapy

If a testis has not concluded its descent at the age of six months (corrected for gestational age), and since spontaneous testicular descent is unlikely to occur after that age, surgery should be performed within the subsequent year, and by age eighteen months at the latest [72]. In addition, early orchidopexy can be followed by partial catch-up testicular growth, which is not the case in delayed surgery [83]. All these findings recommend performing early orchidopexy between the ages of six and twelve months [70]. But despite early and successful orchiopexy within the first year of life up to 25% of boys with non-syndromic undescended testes may be at risk for infertility based on hormonal and histological data, as a published series on 333 boys showed. This is especially true for bilateral cases, but in addition in about 5% of unilateral cases reduced numbers of germ cells were detected in testicular biopsies as well [86].

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 [87].

3.2.4.2.1.1 Inguinal orchidopexy

Inguinal orchidopexy is a widely used technique with a high success rate of up to 92% [88]. 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 [89]. 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 epididimis to the testis can be judged and described in the protocol. Some boys have a significant dissociation between testis and epididymis which is prognostically bad for fertility. Finally, the mobilised testicle needs to be placed in a sub-dartos pouch within the hemi-scrotum without any tension. If 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 [90]. With regard to fixation sutures, if required, they should be made between the tunica vaginalis and the dartos musculature [91]. 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 [92].

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 [93]. 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 [94]. 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% [87]. Another systematic review and meta-analysis revealed similar outcome data regarding post-operative complications, including wound infection, testicular atrophy, testicular reascent, and hernia for palpable low positioned undescended testes. The only significant difference was the shorter operative time [95].

3.2.4.2.2 Non-palpable testes

For non-palpable testes, surgery must clearly determine whether a testis is present or not [96]. 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 [97]. Subsequent removal or orchidolysis and orchidopexy can be carried out using the same approach to achieve the therapeutic aims [98]. Some tend to start with inguinal surgical exploration, with possible laparoscopy during the procedure [99]. 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 [100].

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%) [101].

If there is a vanishing testis, the procedure is finished once blind-ending spermatic vessels are clearly identified. If the vessels enter the inguinal canal, an atrophic testis may be found upon inguinal exploration or a healthy testis that needs to undergo standard orchidopexy [102]. A peeping testis can be placed down in the scrotum laparoscopically or via an inguinal incision [103]. 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 [104]. Under such circumstances, a Fowler-Stephens orchidopexy may be an option [105] (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. 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 [106]. Due to the nature of these approaches the testis is at risk of hypotrophy or atrophy if the collateral blood supply is insufficient [107]. The testicular survival rate in the one-stage Fowler-Stephens technique varies between 50 and 65% based on post-operative Doppler-ultrasound findings [108]. For two-stage procedures success rates increase up to 90% [109]. The advantages of two-stage orchidopexy, with the second part done usually six months after the first, are to allow for development of collateral blood supply and to create greater testicular mobility [110]. In addition, preservation of the gubernaculum may also decrease the chance of testicular atrophy [111]. 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 [112].

3.2.4.2.3 Complications of surgical therapy

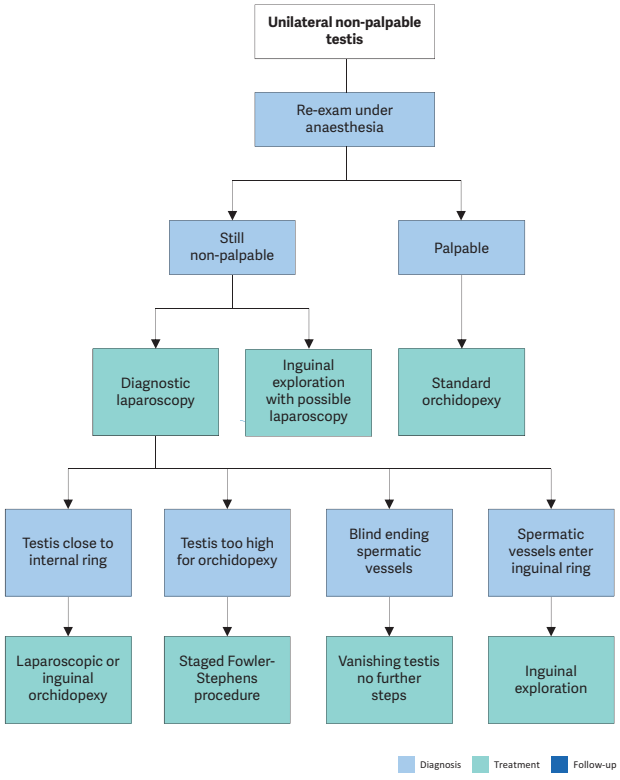
Surgical complications are usually uncommon, with testicular atrophy being the most serious. A systematic review revealed an overall atrophy rate for primary orchidopexy of 1.83%, 28.1% for one-stage Fowler-Stephens procedure, and 8.2% for the two-stage approach [113]. Other rare complications comprise 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 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% [114].

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 [115] is extensively discussed in the literature and seems to be a result of multiple factors, including germ cell loss, impaired germ cell maturation [116], Leydig cell diminution and testicular fibrosis [117].

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 or population

whereas paternity reflects the actual potential of fatherhood [118]. The age at which surgical intervention for an undescended testis occurs seems to be an important predictive factor for fertility later in life. Endocrinological studies revealed higher inhibin-B and lower follicle-stimulating hormone (FSH) levels in men who underwent orchidopexy at two years of age compared to individuals who had surgery later, which is indicative of a benefit of earlier orchidopexy [119]. 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 [120]. 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 [117].

In summary, early surgical correction of undescended testes is highly recommended before twelve months of age, and by eighteen months at the latest for preservation of fertility potential [71].

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 [121]. 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 [122].

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 [123].

3.2.7 *Summary of evidence and recommendations for the management of undescended testes*

Summary of evidence	**LE**
An undescended testis justifies treatment early in life to avoid loss of spermatogenic potential.	2a
A failed or delayed orchidopexy may increase the risk of testicular malignancy later in life.	2a
The earlier the treatment, the lower the risk of impaired fertility and testicular cancer.	2a
In unilateral undescended testis, fertility rate is reduced whereas paternity rate is not.	1b
In bilateral undescended testes, fertility and paternity rates are impaired.	1b
The treatment of choice for undescended testis is surgical replacement in the scrotum.	1b
The palpable testis is usually treated surgically using an inguinal approach.	2b
The non-palpable testis is most commonly approached laparoscopically.	2b
There is no consensus on the use of hormonal treatment.	2b

Recommendations	**Strength rating**
Do not offer medical or surgical treatment for retractile testes instead undertake close follow-up on a yearly basis until puberty.	Strong
Perform surgical orchidolysis and orchidopexy before the age of twelve months, and by eighteen months at the latest.	Strong
Evaluate male neonates with bilateral non-palpable testes for possible disorders of sex development.	Strong
Perform a diagnostic laparoscopy to locate an intra-abdominal testicle.	Strong
Hormonal therapy in unilateral undescended testes is of no benefit for future paternity.	Strong

Offer endocrine treatment in case of bilateral undescended testes.	Weak
Inform the patient/caregivers about the increased risk of a later malignancy with an undescended testis in a post-pubertal boy or older and discuss removal in case of a contralateral normal testis in a scrotal position.	Weak

3.3 Testicular Tumours in prepubertal boys

*3.3.1 **Introduction***

Testicular tumours account for approximately 1-2% of all paediatric solid tumours [124]. Testicular tumours in prepubertal boys differ in several aspects to testicular tumours in adolescent and adult men: they have a lower incidence, they have a different histologic distribution (teratomas and yolk sac tumours are more common and germ cell tumours are less common) and they are more often benign. A epidemiological study showed that in children under the age of 15 years the incidence is highest in Asia (4.2 per million) and South America (5 per million) and lowest in Europe (2.1 per million) and North America (2.5 per million). This is in contrast to the incidence in adolescent and young adults where the highest incidence is in Europe (137.4 per million), and North America (94.9 per million), while a lower incidence was observed in South and Central America (66.5 per million) and Asia (27.1 per million) [125]. For age distribution in prepubertal boys, there is a small peak around the age of two years [126]. Some studies demonstrated that up to 60-75% of the tumours are benign [124, 127-131]. Intratubular neoplasia (TIN) is practically non-existent in children [132-135]. Testicular tumours can generally be classified as germ cell or stromal tumours. One specific tumour type is the gonadoblastoma, which contains germ cell and stromal cell tumour types and will occur almost exclusively in the setting of disorders of sexual differentiation [136].

In the past 30 years, it has clearly been shown, that there is a fundamental difference between testicular tumours in childhood and those in adulthood - not only in terms of the difference and incidence [125] but also in terms of histology [132]. In prepubertal boys, most intratesticular tumours are benign, whereas post puberty the tumours are most likely malignant.

3.3.2 Clinical presentation

Clinical presentation is a painless scrotal mass in more than 90% of the patients, detected by the caregiver, physician or the patient himself. A history of a trauma, pain or hernia is rare. A hydrocele can be found in 15 – 50% [128, 137]. In boys with early onset of puberty (e.g. early penile and prepubic hair growth) as well as high testosterone and low gonadotropin levels, a Leydig cell tumour should be excluded [138].

In patients presenting with a scrotal mass, paratesticular tumours should also be taken into account as a differential diagnosis. However, these are even less common compared to intratesticular tumours. The spectrum of paratesticular tumours includes benign tumours such as leiomyoma, fibroma, lipoma, haemangioma, cystic lymphangioma and lipoblastoma as well as malignant tumours such as the paratesticular rhabdomyosarcoma with an excellent prognosis and the rare melanotic neuroectodermal tumour of infancy with a high recurrence rate [139-142]. As most of them are benign, intra-operative frozen section should be available during surgery. An organ sparing surgical approach is preferred in benign tumours, whereas in malignant tumour standard orchiectomy is carried out.

*3.3.3 **Evaluation***

To confirm the diagnosis, a high-resolution US examination (7.5 – 12.5 MHz), preferably a doppler ultrasound, is required. The detection rate is almost 100% [143-146]. With high-resolution US, microlithiasis - small hyperdense areas without sound shadows - is increasingly seen in prepubertal boys. A meta-analysis showed that only 4 out of 296 boys (< 19 years of age diagnosed with microlithiasis) developed a testicular tumour of whom two previously had a testicular tumour on the opposite or ipsilateral site [147]. If microlithiasis shows up in patients with additional risk factors for testicular tumour, then the caregivers/patients should be informed about the increased risk and encouraged to carry out regular self-examinations - similar to patients treated for undescended testis [148]. There is no evidence, that regular sonographic follow-up is useful [147]. The risk for infertility may be higher in patients with microlithiasis and if these patients have any sign of infertility later, the risk of developing a tumour seems to be higher compared to patients without microlithiasis and infertility [149]. Due to the low incidence of a contralateral tumour, even in cases of testicular microlithiasis, there is no indication for contralateral testicular biopsy in prepubertal boys.

Age should be taken into account, when tumour markers are used. Human chorionic gonadotropin (ß-hCG) is derived from chorion carcinoma, embryonal carcinoma or seminoma. However, these tumours are extremely rare in prepubertal boys and therefore ß-hCG is not useful in prepubertal boys. Alpha-fetoprotein (AFP) has a clear limitation of its sensitivity and specificity in the first months of life [137] and sometimes takes up to

twelve months before the serum concentration reaches the known standard values (< 10 ng/mL) [131, 150]. It is produced by > 90% of yolk sac tumours. Teratomas can also produce AFP, but not to that extent of yolk sac tumours [151]. Alpha-fetoprotein should be measured before any therapeutic intervention (tumour enucleation/ orchiectomy) and ideally should be available at the time of the procedure. Alpha-fetoprotein has a serum biological half-life of five days and should be measured five days after tumour resection/orchiectomy in those with an elevated AFP. There is no urgent need for pre-operative staging, as this has no consequence before the definitive histology is available.

*3.3.4 **Treatment/Management***

If a testicular tumour is suspected, surgery with the option of intra-operative frozen section should be performed. It is not necessary to do this as an emergency procedure. However, in order to confirm the diagnosis and to avoid familial anxiety, the operation should be scheduled as soon as possible, preferably within the next few days. Organ-preserving surgery should be performed, whenever possible. A review article showed that out of 227 patients with organ-sparing surgery only two cases (one in a patient with an epidermoid cyst and one in a patient with a mature teratoma) had a recurrence [152-154].

Orchiectomy could be considered only if normal testicular parenchyma is no longer detectable in the pre-operatively high-resolution ultrasound and/or the AFP is > 100 ng/mL in a > 12-month-old boy: highly suspicious of a yolk sac tumour.

For surgical technique, the Panel is in favour of an inguinal approach. Furthermore, clamping of the vessels has the advantage of a better view, when organ sparing surgery is performed. However, there is no evidence in the literature, that tumour-spread is prevented by clamping the vessels. Whenever possible, testis sparing surgery should be performed along with frozen sections during surgery to confirm the diagnosis (begin vs. malignant tumour) and to confirm if a microscopically margin-negative resection is performed, in which no gross or microscopic tumour remains in the primary tumour bed (R0 resection). In cases of an R0 resection, the tunica is closed and the testis is replaced in the scrotum. In case of R1 resection (removal of all macroscopic disease, but microscopic margins are positive for tumour) confirmed by frozen section in a malignant or potential malignant tumour, an orchiectomy should be performed at the same time of surgery. If the final pathology later demonstrates a R1 resection in a malignant tumour despite intra-operative negative margins on frozen section, an inguinal orchiectomy can safely be performed.

In patients with a malignant tumour (yolk sac tumour, immature teratoma) staging should be performed including an MRI of the abdomen and a CT-scan from the chest. If there is any suspicion of a non-organ confined tumour, the patient should be referred to a paediatric oncologist. In patients with the rare diagnosis of a Granulosa cell tumour, imaging of the abdomen to exclude enlarged lymph nodes is reasonable as this may be a potentially malignant tumour; in those with Sertoli or a Leydig cell tumour, an MRI is recommended, as 10% are malignant and the metastases do not respond very well to chemotherapy or radiation in the adult literature [155, 156]. The TNM classification from 2015 for adult testicular tumours can be used in patients with a malignant tumour [157]. In benign tumours (mature teratoma, epidermoid cysts) no further staging is required.

*3.3.5 **Tumour entities in prepubertal boys***

Teratomas are usually benign in prepubertal children and represent the greatest proportion of intratesticular tumours (around 40%) [124, 158]. They present at a median age of 13 months (0-18 months). Only in adolescent and adults, they should be considered as malignant tumours. Histologically they can consist of a combination of the three primitive embryological germ-cell layers (ectoderm, mesoderm and endoderm). Most of these elements shows microscopically mature elements [159]; however, some immature teratomas in this age group have also been reported [160]. To exclude any malignant potential, like focal areas of a yolk-sac tumour, the entire specimen should be investigated. On US examination a heterogenous picture with some calcification is seen [161] and AFP should be less than 100 ng/mL in an infant. After organ-sparing surgery only one recurrence was reported in the literature [154].

Epidermoid cysts are of ectodermal origin and seem to be related to well-differentiated teratomas; they are always benign [159]. Keratin-producing epithelium is responsible for the keratinised-squamous-epithelial deposits, which appear hyperechogenic in an US [161]. Organ-sparing surgery should be performed and if confirmed by histology, there is no need for surveillance despite the fact that one “recurrence” has been reported thirteen years after diagnosis [153].

Juvenile granulosa cell tumours occur usually in the first year of life, typically within the first six months [162]. They are well circumscribed and have a typical yellow-tan appearance; 2/3 have cystic elements, 1/3 solid [162].

The stroma can be fibrous or fibromyxoid. So far, no recurrence has been reported after organ-sparing surgery [162, 163].

Leydig cell tumours arising from the testosterone producing Leydig cells should be suspected in boys with early onset of puberty with high testosterone and low gonadotropin levels [138]. Patients are usually between six and ten years of age; the tumours are well circumscribed with yellow-brown nodules. In children there are no reports of malignant Leydig cell tumours and after organ sparing surgery, there are no reported recurrences to date [164, 165]. In the adult literature, there is a malignancy rate of 10% reported and primary retroperitoneal lymphadenectomy should be discussed in cases with enlarged lymph nodes, as these metastases do not respond very well to chemotherapy or radiation [166].

Around 1/5 of the Sertoli-cell tumours occur in children; usually within the first year of life [167]. In the paediatric age group, the large-cell calcifying Sertoli cell tumours (LCCSCT) are the most common tumour variant [168, 169]. They can occur in patients with complex dysplastic syndromes, such as the Carney or Peutz-Jeghers syndrome [169-171]. Except one case report with the histological diagnosis of a malignant LCCSCT [168], all other reported tumours are benign, therefore organ-sparing surgery should be performed.

Yolk sac tumours are the predominant prepubertal malignant germ cell tumours and may represent around 15% of the prepubertal tumours in boys [124]. They also have a number of other names: endodermal sinus tumours, juvenile embryonal carcinoma, clear cell carcinoma, orchioblastoma, vitellineum, archenteronoma and sometimes extraembryonal mesoblastoma [172]. They are histologically mostly solid, yellow-grey tumours. They occur usually within the first two years of life [173]. Up to 80-85% of the tumours are organ confined (Stage I) [174]. The tumour usually spreads haematogenously (chest). Twenty percent of those with Stage I disease may develop visible metastasis in 20% within the next two years. In a German study, 14 out of 91 patients with Stage I had a recurrence after observation – all were cured by chemotherapy alone. Four out of five with metastatic disease initially, were cured by chemotherapy after radical orchiectomy [175]. In a published series from China, 21 out of 90 paediatric patients with a Stage I yolk sac tumour received primary chemotherapy. One of the 21 had a recurrence, whereas 29 out of 69 who underwent surveillance after initial orchiectomy had a recurrence. The overall four-year survival rate was 97.8% [173], almost the same recurrence rate has also been reported by American oncology groups [176, 177]. Therefore in patients with Stage I disease (no metastatic disease in the MRI-abdomen and CT scan of the chest as well as normal age-adapted AFP values) close follow-up together with the paediatric oncologists including AFP every two to three months and MRI of the abdomen is recommended, at least for the first two to three years [137]. This is especially recommended in those with invasions of the lymphatic vessels, as this has been shown to be a prognostic factor in one of the recent series [173]. In cases of recurrence, chemotherapy should be performed by paediatric oncologists according to national study protocols.

3.3.6 ***Follow-up***

Regular US examination is recommended in the follow-up period to detect any recurrence and/or other abnormalities. As there are only a few studies with recurrence after testicular sparing surgery or orchiectomy, no clear recommendation can be made concerning the interval and the duration of follow-up. However, doing an US examination every three to six months within the first year seems reasonable, as few recurrences have been detected at this time and the rate of atrophy is extremely low after organ-sparing surgery [152]. Only in patients with a malignant tumour, regular follow-up examination after the first year of surgery seems reasonable (see above). The follow-up in patients with a Leydig cell tumour should include endocrinological examinations. Using the SEER data base, the five-year relative survival for testicular malignancies for patients < 14 years of age diagnosed with localised testicular cancer was 97.4%, and for those with distant disease 72.6% [178].

3.3.7 ***Congenital Adrenal Hyperplasia***

Boys with a congenital adrenal hyperplasia (CAH) represent a special group. Up to a third of the patients have so-called testicular adrenal rest tumours (TARTs) This proportion increase with age [179, 180]. It is most likely to be ectopic adrenal cells, which are growing under pathological stimulation from Adrenocorticotropic Hormone (ACTH) [181]. They have no malignant potential, but they can have a lasting impact on fertility by displacing the normal testicular parenchyma [181, 182]. These patients should be offered US screening and advice on fertility with the option of cryopreservation [182]. As far as is known, no malignant tumour has been described in patients with a typical TART. As a result, the indication for surgical intervention in these patients to rule out a malignant tumour should be offered very cautiously.

Summary of evidence	LE
Testicular tumours in prepubertal boys have a lower incidence and a different histologic distribution compared to the adolescent and adult patients.	2a
In prepupertal boys up to 60-75% of testicular tumours are benign.	3

Recommendations	Strength rating
High-resolution ultrasound (7.5 – 12.5 MHz), preferably a doppler ultrasound, should be performed to confirm the diagnosis.	Strong
Alpha-fetoprotein (AFP) should be determined in prepubertal boys with a testicular tumour before surgery.	Strong
Surgical exploration should be done with the option for frozen section, but not as an emergency operation.	Strong
Organ-preserving surgery should be performed in all benign tumours.	Strong
Staging (MRI abdomen /CT chest) should only be performed in patients with a malignant tumour to exclude metastases.	Strong
Magnetic resonance imaging should only be performed in patients with the potential malignant Leydig or Sertoli-cell-tumours to rule out lymph node enlargement.	Weak
Patients with a non-organ confined tumour should be referred to paediatric oncologists post-operatively.	Weak

3.4 Fertility preservation in children and adolescents

The continuous increase in the incidence of paediatric cancers and post-treatment survivorship over the years, coupled with the further development of potentially gonadotoxic therapies, has contributed to the recognition and rapid endorsement of fertility preservation counselling for prepubertal children and adolescents. Patients and caregivers should be informed not only about the impact of gonadotoxic treatments on future fertility but also about fertility-preservation options and their risk-benefit ratio. There are also a number of non-oncological congenital anomalies where fertility preservation can become an issue.

This chapter focuses on basic information on cryopreservation indications and options for paediatric urologists. For more detailed information, we refer to specific guidelines on this topic [183-185].

3.4.1 Ovarian tissue cryopreservation in prepubertal and adolescent girls

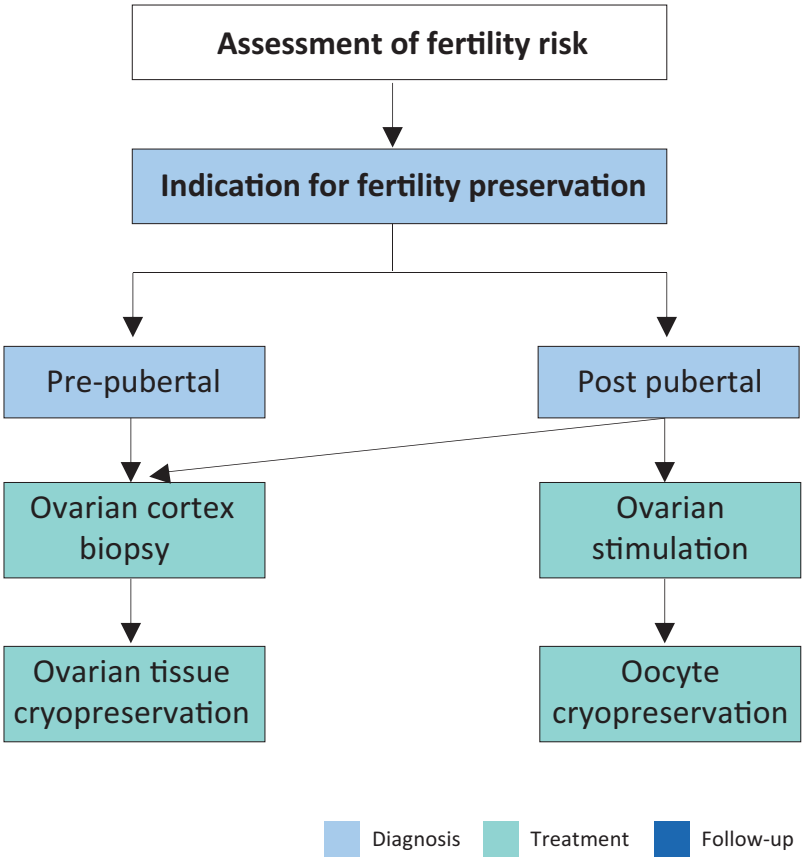
Infertility in the paediatric and adolescent population can result from direct gonadal damage from surgery, or gonadal toxicity as a result of chemotherapy or radiation [183]. Frequent indications requiring gonadotoxic therapy include solid tumors, leukemia and benign indications, such as hemoglobinopathies [186]. First-line chemotherapy does not appear to affect the number of primordial follicles [187], rather, it seems to have a significant effect on the health, density and functionality of follicles [188], resulting in a reduction of 10-30% of ovarian reserve, depending on age and menarchal status [189]. The indication and options for fertility preservation should ideally be discussed in a paediatric multidisciplinary fertility preservation team and should consider the toxicity of the planned therapy, the age and menarchal status as well ethical and financial issues [190, 191].

In paediatric and adolescent patients, ovarian tissue retrieval is performed by removal of an entire ovary (or partial ovariectomy) by laparoscopy [192], or in the setting of a laparotomy for surgery of the primary tumor [186, 193]. It is advised to combine these interventions with other medically indicated procedures to minimize any additional anesthetic risks and costs [194]. In postpubertal patients and in the setting of benign disease, oocyte retrieval following prior ovarian stimulation can be performed [195-198]. For patients undergoing brachytherapy of the pelvic region, the technique of temporary laparoscopic ovarian transposition has been described [199].

Ovarian tissue can be re-implanted orthotopically or heterotopically. For fertility purposes, orthotopic transplantation includes implanting ovarian tissue into the peritoneal cavity, the remaining contralateral ovary, the ovarian fossa or the broad peritoneal ligament [200]. Heterotopic transplantation includes transplantation of ovarian tissue into other locations, such as the subcutaneous abdominal wall, the rectus muscle and the forearm. This technique can be used for the recovery of natural endocrine function [200]. The utilization rate of ovarian tissue for ovarian cortex autotransplantation in the pediatric population has been reported to be as low as 2.2-5% [197, 201, 202]. A large case series demonstrated that transplantation of prepubertal cryopreserved

ovarian tissue resulted in induction of spontaneous puberty and pregnancies in a few reported cases. However, there are only a few cases with long-term outcomes reported in the literature [203, 204].

Figure 3: Ovarian tissue cryopreservation for girls and adolescents



Adapted from Anderson et al. [198]

3.4.2 Cryopreservation in prepubertal and adolescent boys

The increase in the incidence of paediatric cancers and post-treatment survivors has also contributed to studies for fertility preservation in prepubertal boys. Gonadoprotective measures aiming at protecting the survival and function of immature germ cells in prepubertal testes, which are highly susceptible to irradiation and chemotherapy, should be the first aim [205]. Attenuation of externally scattered irradiation from fields close to the testes by gonadal shielding has been shown to be effective with respect to testicular growth in survivors [206, 207]. In patients undergoing brachytherapy in the region of the genitals, temporary testicular transposition has been described as a method for fertility preservation [208].

Sperm cryopreservation via masturbation or penile vibration should be the first option in non-azoospermic post pubertal boys. Techniques such as electro ejaculation should only be discussed in very specific circumstances. Cryopreservation of immature testicular tissue, containing spermatogonial stem cells, as a fertility preservation option for this population is still experimental and should be carefully explained to caregivers and patients by a multidisciplinary team [205]. Testicular biopsy procedures do not seem to affect fertility potential due to surgical complications or due to disruption of the blood-testicular barrier, however further studies on this topic are needed [209].

Additional anaesthesia-related risks for testicular sampling should be avoided if possible. The procedure can be combined with any other intervention requiring anaesthesia whenever possible [205].

For benign conditions such as Klinefelter Syndrome, with the potential risk of germ cell loss prior to puberty, bilateral undescended testes cryopreservation has been proposed, but remains controversial and experimental [210-212].

Even though experimental advances have been achieved in non-human primates, many challenges remain to be addressed for prepubertal testes before clinical application.

3.4.3 *Summary of evidence and recommendations fertility preservation in children and adolescents*

Summary of evidence
It is advised to combine any fertility preservation intervention with other medically indicated procedures to minimize additional anesthetic risks and costs.
Ovarian tissue cryopreservation can be used for fertility preservation in pre- and postpubertal girls.
Cryopreservation of immature testicular tissue, containing spermatogonial stem cells, as a fertility preservation option for this population is still experimental and should be well explained to caregivers and patients by a multidisciplinary team.

Recommendations	Strength rating
Inform patients and caregivers about the impact of gonadotoxic treatments on future fertility and about fertility preservation options and their risk-benefit balance.	Strong
Discuss the indications and options for fertility preservation in a pediatric multidisciplinary fertility preservation team and consider the toxicity of the planned therapy, the age and pubertal status as well ethical and financial issues.	Strong

3.5 Hydrocele

3.5.1 ***Epidemiology, aetiology and pathophysiology***

Hydrocele is defined as a collection of fluid between the parietal and visceral layers of the tunica vaginalis [213]. In males congenital hydrocele is based on failed obliteration of the processus vaginalis between the inguinal canal and scrotum. Similarly, although more rare, in females hydrocele can occur with failed obliteration of the canal of Nuck, a protrusion of peritoneum in the female inguinal canal. There are various types of congenital hydrocele. In communicating hydrocele, intraperitoneal fluid passes into the scrotal tunica vaginalis due to persisting patency of the processus vaginalis (PPV). This must be differentiated from inguinal hernia in which the processus vaginalis is wide enough to allow passage of abdominal viscera or omentum [213]. If obliteration of the processus vaginalis occurs with focal patency of the mid-portion, a hydrocele of the cord occurs. The exact time of spontaneous closure of the inguinal processus vaginalis is not known. Processus vaginalis is present in approximately 80-94% of newborns and in 20% of adults [214]. Scrotal hydroceles without associated patency of the inguinal processus vaginalis may be encountered in newborns [215]. However, such non-communicating hydroceles, are often acquired and based on an imbalance between the secretion and re-absorption of lymphatic fluid, and thus can be found secondary to minor trauma, testicular torsion, epididymitis, varicocele operation (due to ligation of the lymphatics) or may appear as a recurrence after hydrocele repair. Rarely a hydrocele may have an intra-abdominal component, positioned ventral or dorsal to the bladder, the so-called abdominoscrotal hydrocele (ASH). This is considered to be a scrotal hydrocele with an hourglass-shaped extension reaching into the abdomen via the inguinal ring. Abdominoscrotal hydrocele may be associated with testicular dysmorphism related to increased pressure [216, 217].

3.5.2 ***Diagnostic evaluation***

The classic description of a communicating hydrocele is that of a hydrocele that fluctuates in size, and is usually related to ambulation. It may be diagnosed by history-taking and physical investigation. The presence of contralateral disease should be addressed during the initial consultation [214]. 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 [218, 219]. In hydroceles the swelling is smooth and usually not tender. If there are any doubts about the character of an intrascrotal mass or if the testis is not palpable, scrotal US should be considered, which 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 [220]. Presence of ASH is suggested by a tense hydrocele or palpable abdominal extension upon compression of the scrotal part of the hydrocele, and can be confirmed by US [217].

3.5.3 ***Management***

Conservative management

In the majority of infants, observation is warranted at least within the first twelve months because of the tendency of spontaneous resolution [221]. The rate of resolution decreases with age, with 92% resolution below one year old and 43% above three years [222, 223]. Initial observation poses little risk as progression to hernia is rare and does not result in incarceration [221]. There is no evidence that hydrocele risks testicular damage [223]. In acquired hydrocele, suggestive of a non-communicating hydrocele, there is still a reasonable chance

of spontaneous resolution (75%) and expectant management of six to nine months is recommended [224]. In ASH the rate of spontaneous resolution appears lower, although it has been reported [225]. In exemption to the above, the suspicion of a concomitant inguinal hernia or underlying testicular pathology necessitates early surgery [226]. In other cases initial conservative treatment may reduce the number of procedures without increasing morbidity, however persistence of hydrocele is an indication for surgical correction.

Surgical treatment

In the paediatric age group, surgical correction consists of inguinal ligation of the patent processus vaginalis via inguinal incision with the distal stump being left open. In hydrocele of the cord the cystic mass is excised or unroofed [219, 227, 228]. In expert hands, the incidence of testicular damage during hydrocele or inguinal hernia repair is very low. Laparoscopic hernia repair with percutaneous ligation of the patent inguinal processus vaginalis is a minimally invasive alternative to open inguinal herniorrhaphy [229, 230]. In line with these techniques, various laparoscopic techniques for hydrocele correction have been described. No technique appears to be superior [214].

Laparoscopic correction of a contralateral patent processus may be considered, however a recent meta-analysis found insufficient evidence to recommend this for inguinal hernia [214] and hydrocele was not reported. The incidence of patent contralateral processus appears much higher than the percentage of children developing metachronous hernia (63% vs 8%) [214]. Thus, to prevent metachronous inguinal hernia the number needed to treat is relatively high (NNT=18) [231]. For acquired, non-communicating hydrocele the scrotal approach (Lord or Jaboulay/Winkelmann technique) is used.

In ASH most case series describe resection of the abdominal component which is connected to the scrotal, but not to the inguinal processus vaginalis. The incidence of complications for this procedure is higher than in regular hydrocele repair [225] and can result in testicular loss and atrophy, causing some to question if resection is necessary [217, 225]. Larger series are needed to assess optimal management. Testicular dysmorphism may recover following surgery [216]. Sclerosing agents should not be used because of the risk of chemical peritonitis in communicating processus vaginalis [219].

*3.5.4 **Summary of evidence and recommendations for the management of hydrocele***

Summary of evidence
In the majority of infants, surgical treatment of hydrocele is not indicated within the first twelve months due to the tendency for spontaneous resolution. Little risk is taken by initial observation as progression to hernia is rare.
In acquired hydrocele initial expectant is recommended, unless hernia or testicular pathology are suspected.
In the paediatric age group, an operation would generally involve ligation of the patent processus vaginalis via inguinal incision.

Recommendations	**Strength rating**
Observe hydroceles in the majority of infants prior to considering surgical treatment.	Strong
Perform early surgery if there is suspicion of a concomitant inguinal hernia or underlying testicular pathology.	Strong
Perform ultrasound in case of doubt about the character of an intrascrotal mass, or suspicion of an abdominoscrotal hydrocele.	Strong
Close the processus vaginalis at the inguinal ring.	Strong
Do not use sclerosing agents in children with hydroceles, because of the risk for chemical peritonitis.	Strong

3.6 Acute scrotum

*3.6.1 **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 [232-237]. 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) [238-250]. Trauma can also be a cause of acute scrotum due to post-traumatic haematomas, testicular contusion, rupture, dislocation or torsion [251-256]. 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 [257].

In this chapter testicular torsion and epididymitis are discussed, while recurrent epididymitis is discussed in the chapter dealing with infections. Torsion of the testis occurs most often in the neonatal period and around puberty, whereas torsion of the appendix testis occurs over a wider age range [258]. Epididymitis affects two age groups: less than one year and twelve to fifteen years [259, 260]. One study predicted the annual incidence of epididymitis around 1.2 per 1,000 children [261].

Perinatal torsion of the testis most often occurs prenatally. Bilateral torsion comprises 11-21% of all perinatal cases [262]. Most cases of perinatal torsion are extravaginal, in contrast to the usual intravaginal torsion which occurs during puberty.

*3.6.2 **Diagnostic evaluation***

Patients usually present with scrotal pain, except in neonatal torsion. The sudden onset of invalidating pain in combination with vomiting is typical for torsion of the testis or appendix testis [263, 264].

In general, the duration of symptoms at presentation is shorter in testicular torsion (69% present within twelve hours) and torsion of the appendix testis (62%) compared to epididymitis (31%) [234, 235, 260]. Prepubertal males are more likely to present with atypical symptoms and delayed presentation and diagnosis, leading to delayed surgical intervention and a higher rate of orchiectomy, compared to postpubertal boys [265].

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, in case of torsion of the appendix testis there may be isolated tenderness of the superior pole of the testis [260].

An abnormal (horizontal) position of the testis is more frequent in testicular torsion than epididymitis [234]. Looking for absence of the cremasteric reflex is a simple method with 100% sensitivity and 66% specificity for testicular torsion [259, 264] (LE: 3). Elevation of the scrotum may reduce complaints in epididymitis, but not in testicular torsion.

Fever occurs more often in epididymitis (11-19%). The classical sign of a “blue dot” was found only in 10-23% of patients with torsion of the appendix testis [233, 234, 259, 266]. In many cases, it is not easy to determine the cause of acute scrotum based on history and physical examination alone [232-237, 259, 266]. A positive urine culture is only found in a few patients with epididymitis [236, 259, 266, 267]. 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, a positive predictive value of 100% and negative predictive value of 97.5% [268-273] (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 [270, 274]. 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 [270]. A comparison with the other side should always be done.

Better results were reported using high-resolution US (HRUS) for direct visualisation of the spermatic cord twist with a sensitivity of 97.3% and specificity of 99% [270, 275] (LE: 2). A so-called positive whirlpool sign (the presence of a spiral-like pattern), has a pooled sensitivity and specificity of 0.73 (95% CI; 0.65-0.79) and 0.99 (95% CI; 0.92-0.99), respectively, and may be viewed as a definitive sign for testicular torsion. But its role in neonates is limited [276].

Scintigraphy and, more recently, dynamic contrast-enhanced subtraction MRI of the scrotum also provide a comparable sensitivity and specificity to US [277-280]. 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 [266].

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 [281]. 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 [236, 259, 261].

*3.6.3 **Management***

3.6.3.1 Epididymitis

In pre-pubertal boys, the aetiology is usually unclear, with an underlying pathology in about 25%. A urine culture is usually negative, and unlike in older boys, a sexually transmitted disease is very rare.

Antibiotic treatment, although often started, is not indicated in most cases unless urinalysis and urine culture show a bacterial infection [261, 282]. Epididymitis is usually self-limiting and with supportive therapy (i.e. minimal physical activity and analgesics) heals without any sequelae (LE: 3). However, bacterial epididymitis can be complicated by abscess or necrotic testis and surgical exploration is required [283].

3.6.3.2 Testicular torsion

Manual detorsion of the testis is done without anaesthesia, and should be attempted in all patients if possible, because it is associated with improved surgical salvage rates [284]. It should initially be done by outward rotation of the testis - like opening a book -, 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 [285] (LE: 3). Doppler US may be used for guidance [286]. Bilateral orchiopexy is still required after successful detorsion. This should not be done as an elective procedure, but rather immediately following detorsion. One study reported residual torsion during exploration in 17 out of 53 patients, including eleven patients who had reported pain relief after manual detorsion [285, 287].

External cooling before exploration may be effective in reducing ischaemia reperfusion injury and preserving the viability of the torsed and the contralateral testis [288]. Medical treatments aimed at limiting such injury remain experimental [289-292].

Torsion of the appendix testis can be managed non-operatively with the use of anti-inflammatory analgesics (LE: 4). During the six-week follow-up, clinically and with US, no testicular atrophy was revealed. Surgical exploration is done in equivocal cases and in patients with persistent pain [273]. Although metachronous torsion of the appendix testis may occur in up to 8.5%, it is not necessary to explore the contralateral side, given the benign nature ot the problem. Besides it has been demonstrated that the NNT is 24 [293].

3.6.3.3 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 [294]. 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, a necrotic or severely atrophied testis was found in all cases of torsion > 360° and symptom duration > 24 hours [295].

Early surgical intervention with detorsion (mean torsion time less than thirteen hours) was found to preserve fertility [296]. Urgent surgical exploration is mandatory in all cases of testicular torsion within 24 hours of symptom onset. In patients with testicular torsion > 24 hours, exploration may be performed as a semi-elective exploration procedure [294, 295] (LE: 3), unless there is a clear history of torsion-detorsion in which urgent exploration should still be considered. In case of prolonged torsion (> 24 hours) it is still subject to debate whether the surgically detorsed testis should be preserved. An alternative to detorsion and fixation may be to perform orchiectomy. A study found that sperm quality was preserved after both orchiectomy and orchidopexy in comparison to normal control men, although orchiectomy resulted in better sperm morphology [297] Incision of the tunica albuginea with tunica vaginalis graft to prevent or treat compartment syndrome has also been suggested [298].

In neonates with signs of testicular torsion at birth the duration of symptoms will not be clear. The decision to perform surgical exploration should be weighed against the general condition of the child. In this age group the operation can safely be done under spinal anesthesia. New onset of symptoms of testicular torsion in neonates should be considered a surgical emergency similar to older boys.

During exploration, fixation of the contralateral testis is also performed. It is good clinical practice to also perform fixation of the contralateral testis in prenatal and neonatal torsion, although there is no literature to support this, and to remove an atrophied testicle [299]. Recurrence after orchidopexy is rare (4.5%) and may occur several years later. There is no consensus recommendation about the preferred type of fixation and suture material [300].

3.6.4 ***Follow-up***

Patients require follow-up mainly for fertility issues and hormonal consequences. Despite timely and adequate detorsion and fixation of the testicle, up to half of the patients may develop testicular atrophy, even when intraoperatively assessed as viable, and should be counselled accordingly [301, 302].

3.6.4.1 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% [279]. Although, 30% of affected testicles with mumps orchitis show a degree of atrophy, long-term outcome in terms of fertility is not conclusive [303].

A study showed a normal pregnancy rate after unilateral testicular torsion, with no difference between the patients undergoing orchidopexy and those after orchidectomy [304].

3.6.4.2 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 [294]. Early surgical intervention (mean torsion time less than thirteen hours) with detorsion was found to preserve fertility, but a prolonged torsion period (mean 70 hours) followed by orchiectomy jeopardised fertility [296].

Subfertility and infertility are consequences of direct injury to the testis after the torsion. This is caused by the cut-off of blood supply, but also by post-ischaemia-reperfusion injury that is caused after the detorsion when oxygen-derived free radicals are rapidly circulated within the testicular parenchyma [294].

3.6.4.3 Androgen levels

Even though the levels of FSH, luteinising hormone (LH) and testosterone are higher in patients after testicular torsion compared to normal controls, endocrine testicular function remains in the normal range after testicular torsion [297].

3.6.4.4 Unanswered questions

Although testicular torsion is a common problem, the mechanism of neonatal and prenatal torsion is still not exactly known, as well as whether fixation of the contralateral testicle in these cases is really necessary. The influence of an atrophied testicle on fertility is also unclear.

Summary of evidence	**LE**
Diagnosis of testicular torsion is based on presentation and physical exam.	-
Doppler US is an effective imaging tool to evaluate acute scrotum and comparable to scintigraphy and dynamic contrast-enhanced subtraction MRI.	2a
Neonates with acute scrotum should be treated as surgical emergencies.	3

Recommendations	**Strength rating**
Testicular torsion is a paediatric urological emergency and requires immediate treatment.	Strong
In neonates with testicular torsion perform orchidopexy of the contralateral testicle. In prenatal torsion the timing of surgery is usually dictated by clinical findings.	Weak
Base the clinical decision on physical examination. The use of Doppler ultrasound to evaluate acute scrotum is useful, but this should not delay the intervention.	Strong
Manage torsion of the appendix testis conservatively. Perform surgical exploration in equivocal cases and in patients with persistent pain.	Strong
Perform urgent surgical exploration in all cases of testicular torsion within 24 hours of symptom onset. In prenatal torsion the timing of surgery is usually dictated by clinical findings.	Strong

3.7 Hypospadias

*3.7.1 **Epidemiology, aetiology and pathophysiology***

3.7.1.1 Epidemiology

The total prevalence of hypospadias in Europe is 18.6 new cases per 10,000 births (5.1-36.8) according to the EUROCAT registry-based study. This incidence was stable over the period of 2001 to 2010 [305, 306]. The mean worldwide prevalence of hypospadias according to an extended systematic literature review varies: Europe 19.9 (range: 1-464), North America 34.2 (6-129.8), South America 5.2 (2.8-110), Asia 0.6-69, Africa 5.9 (1.9-110), and Australia 17.1-34.8. There are conflicting data on the recent trends of prevalence – different trends in Europe and an increasing trend in the USA [307, 308].

*3.7.2 **Risk factors***

Risk factors associated with hypospadias are likely to be genetic, placental and/or environmental [305, 306] (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 [306, 309] (LE: 2b).

- An additional family member with hypospadias is found in 7% of families, but this is more predominant in anterior and middle forms [309-312].
- Endocrine disorders can be detected in rare cases.
- Babies with a low birth weight have a higher risk of hypospadias [309-312].
- Over the last 25 years, a significant increase in the incidence of hypospadias has been found.
- Endocrines disruptors are one component of a multi-factorial model for hypospadias.
- The use of oral contraceptives prior to pregnancy has not been associated with an increased risk of hypospadias in offspring, but their use after conception increased the risk of middle and posterior hypospadias [310-313] (LE: 2a).

*3.7.3 **Classification systems***

Hypospadias are usually classified based on the anatomical location of the proximally displaced urethral orifice:

- distal-anterior hypospadias (located on the glans or distal shaft of the penis and the most commo type of hypospadias);
- intermediate-middle (penile);
- proximal-posterior (penoscrotal, scrotal, perineal).

The pathology may be different after skin release and should be reclassified accordingly. Anatomical location of the meatus may not always be enough to explain the severity and the complex nature of this pathology. Therefore, a simple classification related to severity of the problem, which considers penile length, glans size, shape, urethral plate quality and penile curvature is commonly used. In that classification there are two types: mild hypospadias (glanular or penile isolated hypospadias without associated chordee, micropenis or scrotal anomaly); and severe hypospadias (penoscrotal, perineal hypospadias with associated chordee and scrotal anomalies).

*3.7.4 **Diagnostic evaluation***

Most hypospadias patients are easily diagnosed at birth (except for the megameatus intact prepuce variant which can only be seen after retraction of foreskin). Diagnosis includes a description of the local findings:

- position, shape and width of the orifice;
- presence of atretic urethra and division of corpus spongiosum;
- appearance of the preputial hood and scrotum;
- size of the penis;
- curvature of the penis on erection.

The diagnostic evaluation also includes an assessment of associated anomalies, which are:

- cryptorchidism (in up to 10% of cases of hypospadias);
- open processus vaginalis or inguinal hernia (in 9-15%).

Severe hypospadias with unilaterally or bilaterally impalpable testis, or with ambiguous genitalia, requires a complete genetic and endocrine work-up immediately after birth to exclude DSD, especially congenital adrenal hyperplasia. Urine trickling and ballooning of the urethra requires exclusion of meatal stenosis. The relationship between the severity of the hypospadias and associated anomalies of the upper or lower urinary tract were not confirmed [314] (LE: 3).

*3.7.5 **Management***

3.7.5.1 Indication for reconstruction and therapeutic objectives

Differentiation between functionally necessary and aesthetically feasible operative procedures is important for therapeutic decision making.

The indications for surgery are:

- proximally located (ectopic) meatus causing ventrally deflected or spraying urinary stream;
- meatal stenosis;
- anterior curvature of the penis;
- cleft glans;
- rotated penis with abnormal cutaneous raphe;
- preputial hood;
- penoscrotal transposition;
- split scrotum.

Physical examination should check all anatomic components of the penis and evaluate the degree and nature of abnormality in each component. The examination should evaluate location of the meatus, the degree of

proximal spongiosal hypoplasia, presence and degree of penile curvature, width and depth of the urethral plate, size of the glans, degree of ventral skin deficiency, availability of the foreskin and scrotal abnormalities like penoscrotal transposition and bifid scrotum.

As all surgical procedures carry the risk of complications, thorough pre-operative counselling of the caregiver is crucial.

To achieve an overall acceptable functional and cosmetic outcome, the penile curvature must be corrected and a neo-urethra of an adequate size with opening on the glans formed with proper skin coverage of the penile shaft [315] (LE: 4) (Figure 4). The use of magnifying spectacles and fine synthetic absorbable suture materials (6.0-7.0) are required. As in any penile surgery, exceptional prudence should be adopted with the use of cautery. Bipolar cautery is recommended. Knowledge of a variety of surgical reconstructive techniques, wound care and post-operative treatment are essential for a satisfactory outcome.

3.7.5.2 Pre-operative hormonal treatment

There is a lack of high-quality evidence to support that pre-operative hormonal treatment with androgen stimulation improves surgical outcomes. Yet, this treatment in the form of systemic testosterone, topical testosterone, and derivatives like dihydrotestosterone (DHT) and hCG are commonly being used to increase glans size pre-operatively to allow better tubularisation of the urethral plate and decrease the incidence of glans dehiscence. This treatment is usually limited to patients with proximal hypospadias, a small appearing penis, reduced glans circumference or reduced urethral plate [313, 316, 317]. Studies have shown that it leads to significant enlargement of the glans and shaft of the penis (LE: 1b) [318, 319].

Moderate quality evidence from three randomised studies demonstrate significantly lower rates of urethracutaneous fistulae and re-operation rates in patients who received pre-operative hormonal treatment [320].

Pre-operative testosterone administration is most often well tolerated. Transient side effects on child´s behaviour, increased genital pigmentation, appearance of pubic hair, penile skin irritation and redness, increased erections and peri-operative bleeding have been reported, but no persistent side effects related to hormonal stimulation have been reported in the literature. There is also no evidence about possible effects on bone maturation [317, 320, 321].

There are concerns regarding the negative impacts of testosterone on wound-healing and increased bleeding during surgery. Cessation of therapy is recommended one or two months prior to surgery to avoid adverse effects during or after surgery [322].

3.7.5.3 Age at surgery

The age at surgery for primary hypospadias repair is usually 6-18 (24) months [315, 323, 324] (LE: 3). Age at surgery is not a risk factor for urethroplasty complication in pre-pubertal tubularised incised plate urethroplasty (TIP) repair [323] (LE: 2b). Complication rate after primary TIP repair was 2.5 times higher in adults than in the paediatric group according to a prospective controlled study [325] (LE: 2a).

3.7.5.4 Penile curvature

If present, penile curvature is often released by degloving the penis (skin chordee) and by excision of the connective tissue of the genuine chordee on the ventral aspect of the penis in up to 70% [326]. The urethral plate has well vascularised connective tissue and does not cause curvature in most cases [327, 328]. The residual curvature is caused by corporeal disproportion and requires straightening of the penis, mostly using dorsal midline plication or orthoplasty (modification of the Nesbit plication with or without elevation of the neurovascular bundle). In more severe curvature (> 45°), which is often combined with a short urethral plate requiring transection, ventral penile lengthening is recommended to prevent shortening of the penis. This consists of a ventral transverse incision of the tunica albuginea extending from the 3 to 9 o´clock position patched with tunica vaginalis flap or graft, or in several short ventral corporotomies without grafting (LE: 2b) [329]. After the ventral lengthening, a shorter dorsal midline plication is usually added.

According to a retrospective study, dorsal plication remained significantly associated with recurrent ventral curvature independently of the other factors. Ventral corporeal grafting for severe penile curvature gives good long-term results and safety profiles for erectile function [330] (LE: 2b).

3.7.5.5 Urethral reconstruction

The mainstay of hypospadias repair is preservation of the well-vascularised urethral plate and its use for urethral reconstruction has become standard practice in hypospadias repair [328]. Mobilisation of the corpus spongiosum/ urethral plate and the bulbar urethra decreases the need for urethral plate transection [329] (LE: 2b).

If the urethral plate is wide, it can be tubularised following the Thiersch-Duplay technique. If the plate is too narrow to be simply tubularised, it is recommended relaxing the plate by a midline incision and its subsequent tubularisation according to the Snodgrass-Orkiszewski TIP technique. This technique has become the treatment of choice in distal- and mid-penile hypospadias [331-334]. If the incision of the plate is deep, it is recommended to cover the raw surface with inner preputial (or buccal) inlay graft in primary and secondary repairs [335]. This also enables extension of the incision beyond the end of the plate to prevent meatal stenosis [336, 337] (LE: 2a).

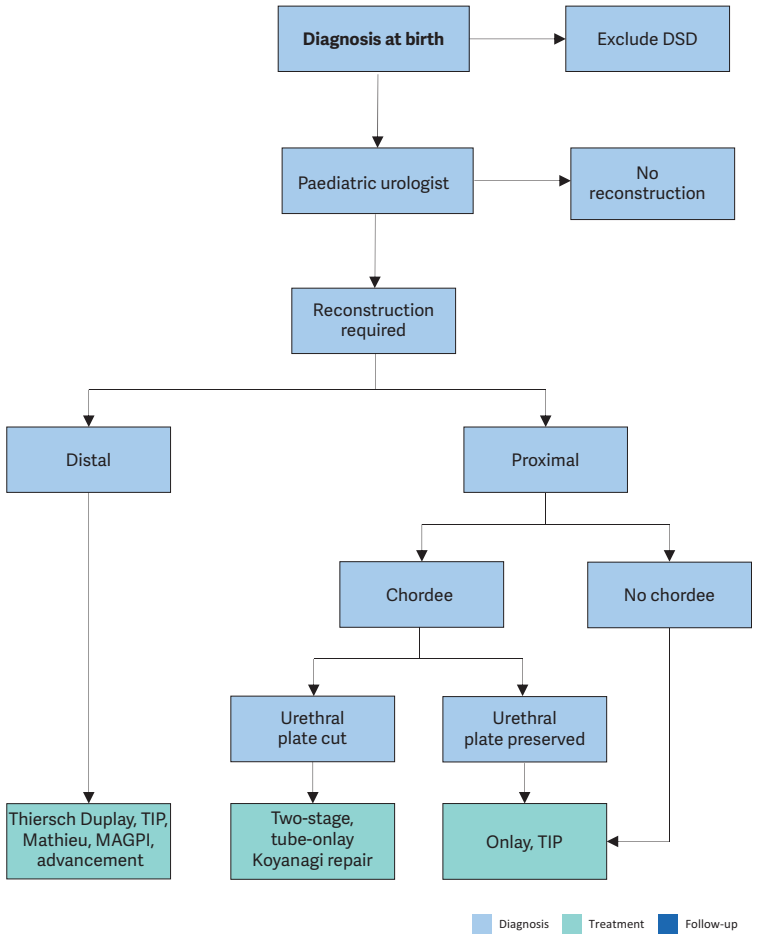
For distal forms of hypospadias, a range of other techniques is available (e.g. Mathieu, urethral advancement) [338] (LE: 2b). The TIP technique has become an option for proximal hypospadias as well [331-334, 339]. However, urethral plate elevation and urethral mobilisation should not be combined with TIP repair because it results in focal devascularisation of the neo-urethra with symptomatic stricture development [340] (LE: 2b). The onlay technique using a preputial island flap is a standard repair, preferred in proximal hypospadias, if a plate is unhealthy or too narrow [326]. An onlay preputial graft is an option for single-stage repair [341] (LE: 2b).

If the continuity of the urethral plate cannot be preserved, single or two-stage repairs are used. For the former, a modification of the tubularised flap (Duckett tube), such as a tube-onlay or an inlay-onlay flap, or onlay flap on albuginea are used to prevent urethral stricture [342-344] (LE: 3); alternatively the Koyanagi-Hayashi technique is used [345-348]. The two-stage procedure has become preferable over the past few years because of lower recurrence of ventral curvature and more favourable results with variable long-term complication rates [337, 342, 349-353].

3.7.5.6 Re-do hypospadias repairs

For re-do hypospadias repairs, no definitive guidelines can be given. All the above-mentioned procedures are used in different ways and are often modified according to the individual findings and needs of the patient.

Figure 4: Algorithm for the management of hypospadias



DSD = disorders of sex development; TIP = tubularised incised plate urethroplasty; MAGPI = meatal advancement and glanuloplasty incorporated.

3.7.5.7 Penile reconstruction following formation of the neo-urethra

Following formation of the neo-urethra, the procedure is completed by glansplasty and by reconstruction of the penile skin. If there is a shortage of skin covering, the preputial double-face technique or placement of the suture line into the scrotum according to Cecil-Michalowski is used. In countries where circumcision is not routinely performed, preputial reconstruction can be considered. Preputial reconstruction carries a risk of specific complications but does not seem to increase the risk of urethroplasty complications [354]. In TIP repair, the use of a preputial dartos flap reduces the fistula rate [331, 332] (LE: 2b).

3.7.5.8 Urine drainage and wound dressing

Urine is drained transurethrally (e.g. dripping stent) or with a suprapubic tube. No drainage after distal hypospadias repair is another option [355, 356]. Circular dressing with slight compression, as well as prophylactic antibiotics during surgery, are established procedures [356] (LE: 4). Post-operative prophylaxis after hypospadias repair has limited benefit and it only reduces the risk of asymptomatic bacteriuria [357-359] (LE: 2b). There is no consensus on duration of stenting and dressing.

3.7.5.9 Outcome

Some studies have tried to determine risk factors for complications after hypospadias repair. An analysis of prospectively collected data found glans size (width < 14 mm), proximal meatal location and re-operation as independent risk factors for urethral complication [356, 360]. Low surgeon volume independently increases the risk of fistula, stricture or diverticulum repair [356, 361] (LE: 3).

A meta-analysis of complication rates of TIP repair found lower complication rates and incidence of re-operations in primary distal repairs (in 4.5%) than in primary proximal repairs (in 12.2%) and in secondary repair (in 23.3%) [331-334, 338, 356]. One should expect a predictable outcome with complication rates below 10% in distal hypospadias (fistula, meatal stenosis, dehiscence, recurrent ventral curvature, and haematoma) [361, 362]. A similar incidence of fistula (3.4-3.6%) can be expected after the Mathieu and TIP repairs of distal hypospadias [339, 363-365].

The complication rates of TIP and onlay repairs of primary severe hypospadias are similar, 24% and 27%, respectively. It is higher in free graft and in preputial island tube urethroplasty [326]. There is no strong evidence to suggest that the use of inlay grafts in TIP repair improves the outcome [366].

The complication rates of single-stage Koyanagi and Hayashi modification repairs go up 61%, according to a comparative study [345, 356]. 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 [364, 367]. A long-term study on two-stage flap repair showed a complication rate of 68% [356]; another study showed a re-operation rate of 28% [337, 356].

3.7.6 ***Follow-up***

Long-term follow-up is necessary up to adolescence to detect urethral stricture, voiding dysfunctions and recurrent penile curvature, diverticula, glanular dehiscence [368]. Up to half of complications requiring re-operation present after the first year post-operatively [369] (LE: 2b).

Obstructive flow curve is common after hypospadias repair and while most are not clinically significant, long-term follow-up is required [370-373] (LE: 2a). Urine flow is significantly lower in patients after hypospadias surgery, especially in those who had corrected chordee, but without significant association with lower urinary symptoms (LUTS) [374] (LE: 2a).

Objective scoring systems have been developed in order to evaluate the results of hypospadias surgery (HOSE) [375] (LE: 2b) and cosmetic appearance (HOPE-Hypospadias Objective Penile Evaluation) [376] (LE: 2a). The Pediatric Penile Perception Score (PPPS) is a reliable instrument to assess penile self-perception in children after hypospadias repair and for appraisal of the surgical result by caregivers and uninvolved urologists [377] (LE: 2a). Cosmetic results were judged more optimistically by surgeons as compared to caregivers using validated tools [378]. Current scoring systems have deficiencies in terms of patient reported outcomes, the long term outcomes and sexual function [379].

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 [380, 381] (LE: 2a-b). Another long-term follow-up of men born with hypospadias revealed, in a controlled study, that these patients are less satisfied with penile cosmetic outcome

according to all parameters of the PPPS; there was a difference in penile length (9.7 vs. 11.6 cm) and more patients had lower maximum urinary flow. More prominent results were found in proximal hypospadias vs. controls [356, 382].

According to a systematic review of long-term patient satisfaction with cosmetic outcomes [383]:

- patient perception of penile size does not differ greatly from the norm;
- patients approaching puberty have a more negative perception and are more critical about the cosmetic outcomes of surgery;
- patients report high levels of perception of deformity and social embarrassment.

There is a wide range of parameters that are measured to assess outcome after hypospadias surgery in the literature. There is a need for age-specific core outcome set [384].

The majority of identified instruments focused on post-operative cosmetic satisfaction, with only one instrument considering urinary function, and no instruments evaluating sexual function and psychosocial sequelae [385].

3.7.7 Summary of evidence and recommendations for the management of hypospadias

Summary of evidence	LE
The suggested age at surgery for primary hypospadias repair is 6-18 (24) months.	3
The therapeutic objectives are to correct the penile curvature, to form a neo-urethra of an adequate size, to bring the new meatus to the tip of the glans, if possible, and to achieve an overall acceptable cosmetic appearance.	4
Androgen stimulation therapy results in increased penile length and glans circumference.	1b
The complication rate is about 10% in distal and 25% in proximal hypospadias one-stage repairs.	3
Higher and variable rates (between 28 and 68%) can occur in two-stage repairs.	2b
Sexual functions are usually well preserved but patients report high levels of perception of deformity and social embarrassment.	

Recommendations	Strength rating
At birth, differentiate isolated hypospadias from disorders of sex development which are mostly associated with cryptorchidism or micropenis.	Strong
Counsel caregivers on functional indications for surgery, aesthetically feasible operative procedures (psychological, cosmetic indications) and possible complications.	Strong
In children diagnosed with proximal hypospadias and a small appearing penis, reduced glans circumference or reduced urethral plate, pre-operative hormonal androgen stimulation treatment is an option and the body of evidence to accentuate its harms and benefits is inadequate.	Weak
For distal hypospadias, offer Duplay-Thiersch urethroplasty, original and modified tubularised incised plate urethroplasty; use the onlay urethroplasty or two-stage procedures in more severe hypospadias. A treatment algorithm is presented (Figure 4). Correct significant (> 30 degrees) curvature of the penis.	Weak
Ensure long-term follow-up to detect urethral stricture, voiding dysfunctions and recurrent penile curvature, ejaculation disorder, and to evaluate patient´s satisfaction.	Strong
Use validated objective scoring systems to assist in evaluating the functional and cosmetic outcome.	Strong

3.8 Congenital penile curvature

3.8.1 Epidemiology, aetiology and pathophysiology

Congenital penile curvature presents penile bending of a normally formed penis due to corporal disproportion. The incidence at birth is 0.6% and congenital penile curvature is caused by asymmetry of the cavernous bodies and an orthotopic meatus [386] because of developmental arrest during embryogenesis [387]. On the other hand, the incidence of clinically significant congenital penile curvature is much lower, because the extent of the curvature and its associated sexual dysfunction varies widely [388]. Most of the cases are ventral deviations (48%), followed by lateral (24%), dorsal (5%), and a combination of ventral and lateral (23%) [389]. Most ventral

curvatures are associated with hypospadias due to chordee or ventral dysplasia of cavernous bodies [390]. Similarly, dorsal curvature is mostly associated with exstrophy/epispadias complex. Congenital penile curvature can decrease sexual quality of life in adults and successful repair can restore patients' psychosocial and sexual wellbeing [391].

Curvature > 30° is considered clinically significant; curvature > 60° may interfere with satisfactory sexual intercourse in adulthood (LE: 4). Minor penile curvature may be the result of ventral penile skin deficiency only and should be distinguished from corporal anomalies. For penile curvature associated with hypospadias or epispadias refer to the relevant chapters.

*3.8.2 **Diagnostic evaluation***

Penile curvature is frequently not documented until later in childhood since the penis only appears abnormal when erect. Patients are usually concerned with the aesthetic and/or functional aspects of their penis [392]. Besides exact history taking to exclude any possibility of acquired penile curvature (e.g. post-traumatic), a thorough clinical examination is mandatory. In addition, photo documentation of the erect penis clearly showing the curvature from different angles serves as a pre-requisite in pre-operative evaluation [393]. The exact degree of curvature is generally determined at the time of surgery using an artificial erection test.

*3.8.3 **Management***

The treatment is surgical, starting with an artificial erection to determine the degree of curvature and to check symmetry after the repair [394]. The ultimate goal of any surgical method used to correct the curvature is to achieve corpora of similar size. Various procedures are in use ranging from simple de-gloving and plication procedures, to corporal rotation, use of free dermal or tunica vaginalis grafts, to complete penile disassembly techniques [395, 396]. Reviews comparing the outcome of Nesbit/modified Nesbit procedures [397] to plication procedures [398] were able to demonstrate that while there is a decreased risk of complications and loss of sensation, it remains unclear whether plication techniques can lead to increased risk of recurrence [399, 400]. Altogether these methods include the risk of post-operative shortening of the penis with an average loss of 2.5 cm in stretched penile length depending on the pre-operative degree of curvature and the type of repair used [401-403].

Recently the non-corporotomy technique has been introduced with promising results enabling correction of any degree of ventral curvature with neither shortening of the penis nor the risk of post-operative erectile dysfunction [404].

*3.8.4 **Summary of evidence and recommendations for the management of congenital penile curvature***

Summary of evidence	**LE**
Isolated congenital penile curvature is relatively uncommon.	2a
Congenital penile curvature is often associated with hypospadias.	2a
Diagnosis is usually made late in childhood.	2a
The penis only appears abnormal when erect.	1b
Congenital penile curvature can cause aesthetic as well as functional sexual problems.	1b
Congenital penile curvature is treated with surgery.	1b
The goal of surgery is to achieve corpora of similar size.	1b

Recommendations	**Strength rating**
Ensure that a thorough medical history is taken and a full clinical examination done to rule out associated anomalies in boys presenting with congenital curvature.	Strong
Provide photo documentation of the erect penis from different angles as a prerequisite in the pre-operative evaluation.	Strong
Perform surgery after weighing aesthetic as well as functional implications of the curvature.	Weak
At the beginning as well as at the end of surgery, perform artificial erection tests.	Strong

3.9 Varicocele in children and adolescents

3.9.1 Epidemiology, aetiology and pathophysiology

Varicocele is defined as an abnormal dilatation of testicular veins in the pampiniformis plexus caused by venous reflux. It is unusual in boys under ten years of age and becomes more frequent at the beginning of puberty. It is found in 14-20% of adolescents, with a similar incidence during adulthood. It appears mostly on the left side (78-93% of cases). Right-sided varicoceles are less common; they are usually noted only when bilateral varicoceles are present and seldom occur as an isolated finding [405-407].

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 [408, 409]. 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 [410, 411]. In 70% of patients with grade II and III varicocele, left testicular volume loss was found. Abnormal reproductive hormonal levels (increased serum levels of FSH and LH, and decreased levels of inhibin B) and semen quality were reported in varicocele patients and were directly related to varicocele severity [412-414]. Severe histological 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 about 20% of adolescents with varicocele, fertility problems will arise [415]. The adverse influence of varicocele increases with time.

3.9.2 Classification systems

Varicocele is classified into 3 grades [416]:

- Grade I - Valsalva positive (palpable at Valsalva manoeuvre only);
- Grade II - palpable (palpable without the Valsalva manoeuvre);
- Grade III - visible (visible at distance).

3.9.3 Diagnostic evaluation

Varicocele, being mostly asymptomatic, is generally noticed by the patient or caregivers, 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. Clinical examination shoud include evaluation of the size of both testicles to detect a smaller testis.

In pre-pubertal boys and in isolated right varicocele, a renal US should be routinely added in order to rule out a secondary varicocele due to any retroperitoneal tumour extending into the renal vein and inferior vena cava.

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 hypotrophic [417]. Venous reflux into the plexus pampiniformis is diagnosed using Doppler US colour flow mapping in the supine and upright position and with valsalva manoeuvre [418]. Venous reflux detected on US only is classified as subclinical varicocele. Severity of reflux on Doppler US was shown to correlate with testicular damage [413].

Sperm analysis in principle allows assessment of testicular function, but the World Health Organization (WHO) parameters are not intended for pre-pubertal patients, and spontaneous improvements of abnormal sperm analyses has been observed in pre-pubertal patients [419]. Moreover, sperm analysis encounters cultural/ethical barriers in children [420]. Therefore, semen analysis in not widely used and it is generally recommended only in older adolescents.

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 [421, 422].

3.9.4 Management

There is no evidence that treatment of varicocele at paediatric age will offer a better andrological outcome than an operation performed later and earlier diagnosis should not convey a more pressing need to intervene [423, 424]. Beneficial effect of pubertal screening and treatment for varicocele regarding the preservation of fertility and final chance of paternity is controversial [425-427]. The recommended indication criteria for correction for varicocele in children and adolescents are [406]:

- varicocele associated with a small testis (this should be confirmed on two subsequent visits performed six months apart) as asynchronous testicular growth can account for a temporary asymmetry also in a considerable number of healthy adolescents [428].

Additional scenarios where varicocele treatment can be considered on a case by case basis include:

- symptomatic varicocele [427]. Pain is present in 2-10% of varicoceles. The association between varicocele and pain is unclear and patients should be informed that pain can persist after varicocelectomy in 20% of cases [429];

- additional testicular condition affecting fertility such as a contralateral testicular condition;
- bilateral palpable varicocele;
- pathological sperm quality (in older adolescents);
- cosmetic reasons related to their scrotal swelling.

A reduced total testicular volume (left + right) in comparison with normal testes is a promising indication criterion, once the normal values are available [414, 423]. 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.

3.9.4.1 Surgical management

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 [430-433].

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 artery 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 [430, 432]. 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 [434, 435].

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 [430, 431, 436, 437]. The methods of choice are subinguinal or inguinal microsurgical (microscopic) repairs, or suprainguinal open or laparoscopic lymphatic-sparing repairs [430, 432, 438, 439]. In the later, intrascrotal/ intratesticular injection of isosulphan blue was recommended to visualise the lymphatic vessels [440, 441]

3.9.4.2 Radiological management

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 [442, 443]. 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 [406, 442, 443].

There is low to moderate level of evidence that radiological or surgical treatment of adolescent varicocele is associated with improved testicular size/growth and sperm concentration. Several authors reported testicular catch-up growth after varicocelectomy in adolescents [444, 445]. An average proportion of catch-up growth of 76.4% (range: 52.6-93.8%) has been found according to a meta-analysis [446] (LE: 2a). However, this may partly be attributable to testicular oedema associated with the division of lymphatic vessels [436]. Improvement in sperm parameters has been demonstrated after adolescent varicocelectomy [421, 447-449]. In one study, microsurgical varicocele repair in adolescents with varicocele significantly increases paternity rates and decreases time to conception post-operatively, but this needs to be confirmed in other series. The ultimate effects on fertility and paternity rates are not known [450].

The Panel conducted a systematic review and meta-analysis regarding the treatment of varicocele in children and adolescents [451]. Of 1,550 articles identified, 98 articles including 16,130 patients were eligible for inclusion (12 RCTs, 47 NRSs and 39 case series). The key findings are summarised in the following paragraphs:

The meta-analysis of the twelve RCTs revealed that varicocele treatment improved testicular volume (mean difference 1.52 ml, 95% CI 0.73-2.31) and increased total sperm concentration (mean difference 25.54, 95% CI 12.84-38.25) when compared with observation. Lymphatic sparing surgery significantly decreased hydrocele rates (p=0.02) and the OR was 0.08 (95% CI 0.01, 0.67). Due to the lack of RCTs, it was not possible to identify a surgical technique as being superior to the others. It remains unclear whether open surgery or laparoscopy is more successful for varicocele treatment (OR ranged from 0.13 to 2.84).

The success rates of the treatment (disappearance of varicocele) were between 85.1% and 100% whereas the complication rates were between 0% and 29% in the included studies. The most common complication reported was hydrocele. Resolution of pain after treatment was more than 90% in the reported series.

The major reason for varicocele recurrence is the persistence of branched spermatic veins that were not ligated during the initial repair. Treatment of recurrence is warranted only in those patients with clinical recurrence that show no improvement in testicular asymmetry or remain symptomatic. Treatment of recurrence can be surgical or via embolisation. Generally, a technique different from the primary repair is recommended to operate in a virgin field [452].

In conclusion, moderate evidence exists on the benefits of varicocele treatment in children and adolescents in terms of testicular volume and sperm concentration. Current evidence does not demonstrate superiority of any of the surgical/interventional techniques regarding treatment success. Lymphatic sparing surgery significantly decreases hydrocele formation. Long-term outcomes, including paternity and fertility, still remain unknown.

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3.9.5 Summary of evidence and recommendations for the management of varicocele

Summary of evidence	LE
Varicocele becomes more frequent at the onset of puberty and is found in 14-20% of adolescents.	3
Testicular problems are reported in up to 20% of patients, but the final effect on paternity is unknown.	3
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.	2
Division of testicular lymphatics leads to hydrocele in up to 40% and to testicular hypertrophy.	
Lymphatic sparing surgery significantly decrease hydrocele rates.	

Recommendations	Strength rating
Examine varicocele in the standing position and classify into three grades.	Strong
Use scrotal ultrasound to evaluate testicular volume and to detect venous reflux in the supine and upright position and during Valsalva maneuver.	Strong
In all pre-pubertal boys with a varicocele and in all isolated right varicoceles, perform standard abdominal ultrasound to rule out a retroperitonal mass.	Strong
Inform caregivers and patients and offer surgery for varicocele associated with a persistent small testis (size difference of > 2 mL or 20%).	Strong
Varicocele treatment can be also considered under the following circumstances: • symptomatic varicocele; • additional testicular condition affecting fertility such as a contralateral testicular condition; • bilateral palpable varicocele; • pathological sperm quality (in older adolescents); • cosmetic reasons related to their scrotal swelling.	Weak
Use some form of optical magnification (microscopic or laparoscopic magnification) for surgical ligation.	Strong
Use lymphatic-sparing varicocelectomy to prevent hydrocele formation.	Strong

3.10 Urinary tract infections in children

3.10.1 Epidemiology, aetiology and pathophysiology

Urinary tract infections (UTIs) represent the most common bacterial infections in children [453-455]. There are several classification systems used to define a UTI. In neonates, the symptoms differ in many aspects from those in infants and children. The prevalence is higher; there is a male predominance; infections caused by other organisms than Escherichia coli are more frequent; and there is a higher risk of urosepsis [456, 457].

In children presenting with urinary symptoms a pooled prevalence of UTI was 7.8% (CI: 6.6-8.9) [456]. The incidence varies depending on age and sex. One meta-analysis showed that in children presenting

with fever 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 [456]. The incidence for boys is highest during the first six months of life (5.3%) and decreases with age to around 2% for the ages 0-6 years. In girls, UTIs are less common during the first six months of life (2%) and incidence increases with age to around 11% for the ages 0-6 years [458].

Associated risk factors for recurrent UTIs include bladder and bowel dysfunction (BBD), vesicoureteral reflux (VUR) and obesity [459-461]. In older children a delay in treatment is more often seen than in younger infants [462]. These risk factors in combination with delay in treatment have been associated with renal scarring [463]. Recurrent febrile UTIs, especially in combination with high-grade VUR, lead to renal scarring [464, 465]. Each new febrile UTI increases the risk of renal scarring with an incidence of renal scarring after the first UTI, of 2.8% (CI:1.2-5.8), 25.7% (CI:12.5-43.3) after the second infection and up to 28.6% (CI:8.4-58.1) after 3 or more febrile UTIs [465].

The leading causative organism for UTIs has been *E. coli*, but other bacteriae have been rising in prevalence. In a large European study *E. Coli* was found in less than 50% of urine cultures. *Klebsiella pneumoniae, Enterobacter spp., Enterococcus spp., Pseudomonas spp., Proteus spp. and Candida spp.* are more frequent in nosocomial infections than in community-acquired UTIs, even though, their prevalence has increased outside of the hospital setting [466]. 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 [467], however, it is less frequent in community-acquired than in nosocomial UTI [467, 468].

*3.10.2 **Classification systems***

There are five widely used classification systems according to; site, severity, episode, symptoms and complicating factors. For acute treatment, site and severity are most important.

3.10.2.1 Classification according to site

Lower urinary tract infection (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 infection (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.

3.10.2.2 Classification according to severity

In a lower 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. Most severe UTIs are upper urinary tract infections.

3.10.2.3 Classification according to episode first/persistent/recurrent/breakthrough

The first UTI may be a sign of anatomical anomalies. 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, urachal cyst, urethral diverticulum, peri-urethral 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.

A breakthough infection in patients under antibacterial prophylaxis is usually caused by resistent bacteria, parental non-compliance and/or severe urogenital anomalies [469, 470].

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.

3.10.2.4 Classification according to symptoms

Children may have typical or atypical symptoms regarding a UTI. In neonates and infants the most commen symptoms are fever, vomiting, lethargy and/or irritability. Infants and children may have non-specific signs such as poor appetite, failure to thrive, lethargy, irritability, vomiting or diarrhoea. Toilet trained children may report cystitis symptoms along with fever/flank pain.

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.

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.

3.10.2.5 Classification according to complicating factors

In uncomplicated UTI, infection occurs in a patient with a morphologically and functionally normal upper and lower urinary tract, normal renal function and competent immune system. This category includes mostly isolated or recurrent bacterial cystitis and is usually associated with a narrow spectrum of infecting pathogens that are easily eradicated by a short course of oral antimicrobial agents. Patients can be managed on an outpatient basis, with an emphasis on documenting resolution of bacteriuria, followed by elective evaluation for potential anatomical or functional abnormalities of the urinary tract [471].

A complicated UTI occurs in children with known mechanical or functional pathology of the urinary tract. Mechanical obstruction is commonly due to the presence of posterior urethral valves, strictures or stones, independent of their location. Functional obstruction often results from lower urinary tract dysfunction (LUTD) of either neurogenic or non-neurogenic origin and dilating 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 [472]. If mechanical or functional abnormalities are present, adequate drainage of the infected urinary tract is necessary.

3.10.3 ***Diagnostic evaluation***

3.10.3.1 Medical history

Medical history includes the question of a primary (first) or secondary (recurring) infection; possible malformations of the urinary tract (e.g. pre- or post-natal US screening); prior operation; family history; and, whether there is constipation or presence of lower urinary tract symptoms (LUTS).

3.10.3.2 Clinical signs and symptoms

Neonates with severe UTI can present with non-specific symptoms (failure to thrive, jaundice, hyperexcitability) and without fever. In neonates it is important to rule out a co-existing meningitis [473]. Urinary tract infection is the cause of fever in 4.1-7.5% of children who present to a paediatric clinic [474, 475]. Septic shock is unusual, even with very high fever. Signs of a UTI may be vague and unspecific in small children, but later on, when they are more than two years old, frequent voiding, dysuria and suprapubic, abdominal or lumbar pain can be detected.

3.10.3.3 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), measurement of body weight and temperature.

3.10.3.4 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 [476].

3.10.3.4.1 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: Although this technique is most often used in daily practice, contamination rates are high with around 50-60% [477]. 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 [478].

(2) Clean-catch urine (CCU) collection: The infant is placed in the lap of a caregiver 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 [479]. Suprapubic tapping alternated with paravertebral lumbar massage can stimulate sponateous voiding [477, 480]. 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% [479, 481]; however, the contamination rate is higher for CCU with up to 26% compared to catheterisation 10% and SPA 1% [477, 482]. In one prospective cohort study in infants below the age of six months, the success rate was 49% and the contamination rate 16% with some differences in the culture results between those obtained by CCU and those by more invasive methods [483].

(3) Transurethral bladder catheterisation: is the fastest and safest method to obtain a reliable urine sample fo microscopic and bacteriological evaluation to rule out or to document a UTI in non-toilet trained infants and children.

(4) Suprapubic bladder aspiration: This is the most invasive but also the most sensitive method to obtain an uncontaminated urine sample in this age group [484, 485]. For suprapubic puncture ultrasound imaging should be performed to asses bladder filling. A two-step procedure where the CCU is screened and a catheter or SPA confirmation of the positive screens is used can lead to a reduction in invasive procedures [477, 482]. In older, toilet-trained children who can void on command, after carefully retracting the foreskin and cleaning the glans penis in boys and spreading the labia and cleaning the peri-urethral area in girls, the use of clean catch, especially midstream urine, could be an acceptable technique for obtaining urine. After cleaning the urethral meatus and perineum with gauze and liquid soap twice, the risk of contamination was reduced from 23.9% (41/171) to 7.8% (14/171) in a randomised trial [486].

3.10.3.4.2 Urinalysis

There are three methods that are commonly used for urinalysis:

(1) Dipsticks: These are appealing because they provide rapid results, do not require microscopy, and are ready to use. Leukocyte esterase (as a surrogate marker for pyuria) and nitrite (which is converted from dietary nitrates by most Gram-negative enteric bacteria in the urine) are the most frequent markers, and are usually combined in a dipstick test. The conversion of dietary nitrates to nitrites by bacteria takes approximately four hours in the bladder [481, 487]. Using only nitrate sticks to screen febrile children < 2 years of age has a too low sensitivity and relevant UTIs can be missed. However, the specificity is high for children at any age [488, 489]. In febrile infants < 90 days old urine dipstick tests using CCU samples can be used for screening for a UTI when nitrites and leukocyte esterase combined are used with a sensitivity of 86% and a specificity of 80% [490].

(2) Microscopy: This is the standard method of assessing pyuria after centrifugation of the urine with a threshold of five white blood cells (WBCs) per high-power field (25 WBC/µL) [491]. In uncentrifuged urine, > 10 WBC/µL has been demonstrated to be sensitive for UTI [492] and this could perform well in clinical situations [493]. However, this is rarely done in an outpatient setting. No significant differences was found between dipsticks and microscopy testing for UTI [489]. A meta-analysis showed, that only microscopy with Gram staining has a higer sensitivity compared to dipsticks [494].

(3) Flow imaging analysis technology: This is being used increasingly to classify particles in uncentrifuged urine specimens [495]. The numbers of WBCs, squamous epithelial cells and red cells correlate well with those found by manual methods [481]. Flow cytometry-based bacterial and leukocyte count analysis when using a cut-off value of 250 bacteria/uL in the presence of leukocyturia has a sensitivity of 0.97 and specificity of 0.91 for diagnosing UTI [496].

3.10.3.4.3 Urine culture

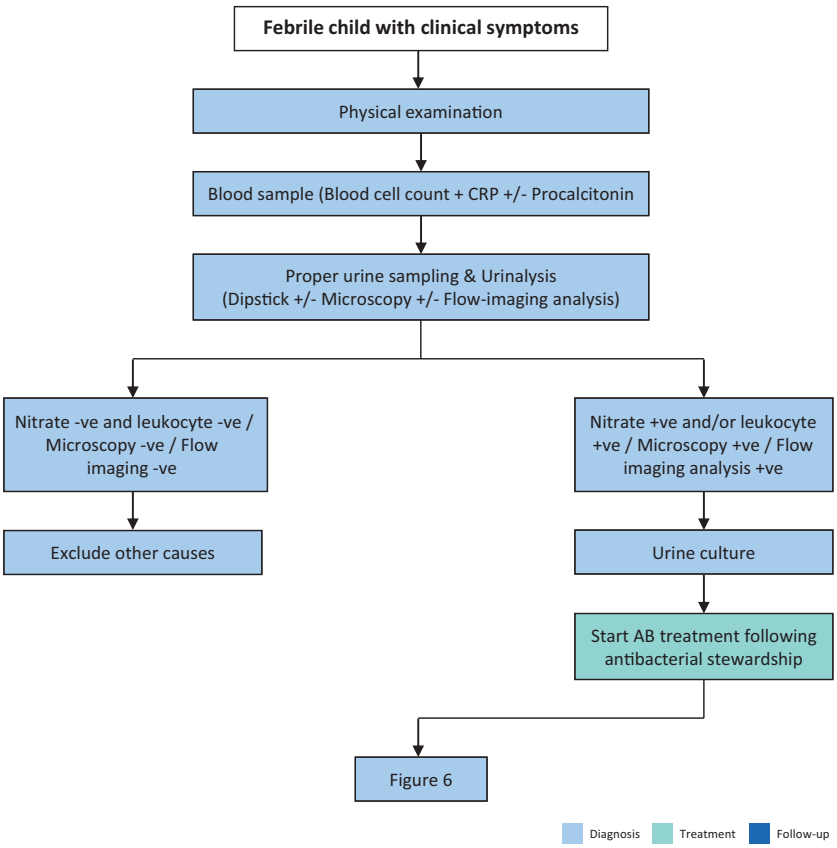
After negative results for dipstick, microscopic or automated urinalysis, urine culture is generally not necessary, especially if there is an alternative source of fever. If the dipstick result is positive, confirmation by urine culture is strongly recommended.

It is unclear what represents a significant UTI. In patients with a severe UTI, ≥ 105 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 [457]. Clean-catch urine, midstream and catheterisation urine cultures can be considered positive as 103 - 104 cfu/mL in a monoculture, and any counts obtained after SPA should be considered as significant. Mixed cultures are indicative of contamination. In febrile children < 4 months of age a cut-off value of 103 cfu/mL can be used when clinical and laboratory findings match and a correct sampling method has been used [497].

A negative culture with the presence of 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.

A flowchart was developed as guidance during the basic diagnostic evaluation and subsequent management of febrile children with clinical symptoms of UTI, Figure 5.

Figure 5: Diagnostic evaluation and subsequent management of a febrile child with clinical symptoms of UTI



CRP = C-reactive protein; AB = antibiotic.

3.10.3.5 Imaging

3.10.3.5.1 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) [478]. When a renal US is performed in all children presenting with a UTI, 7% will have an abnormal US warranting further investigations [498]. The sensitivity to detect high-grade VUR with US was found to be 0.59 (CI: 0.45-0.72) with a specificity of 0.79 (CI: 0.65-0.87) [499]. Renal US should be performed before and after voiding. Post-void residual (PVR) urine should be measured in toilet-trained children to exclude voiding abnormalities as a cause of UTI. Elevated PVR urine volume predicts recurrence of UTIs in toilet-trained children [500]. When peri-renal or psoas abcesses or renal masses are seen on US, it is important to consider xanthogranulomatous pyelonephritis, and subsequent CT imaging is proposed [501].

3.10.3.5.2 Radionuclide scanning/MRI

Changes in dimercaptosuccinic acid (DMSA) clearance during acute UTI indicate pyelonephritis or parenchymal damage, correlated with the presence of dilating reflux and the risk of further pyelonephritis episodes, breakthrough infections [502] 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 [503]. Diffusion-weighted MRI has shown to accurately diagnose acute pyelonephritis and reveal late renal scars and could be an alternative to DMSA; therefore, avoiding radion burden [504]. The average effective radiation dose of a single DMSA scan was 2.84 (1-12) mSv in one study [505]. These findings are different in neonates. After the first symptomatic, community-acquired UTI, the majority of renal units with

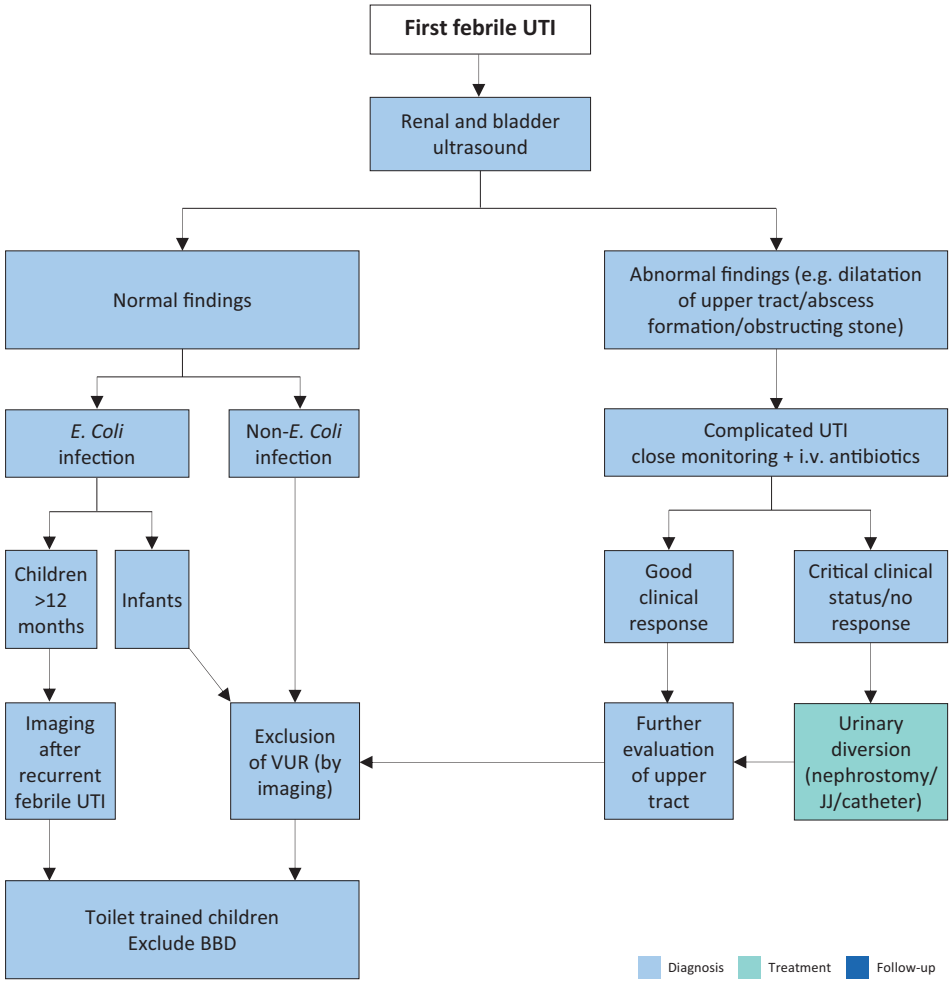
VUR grade III or higher had normal early DMSA scanning [506]. The sensitivity of the DMSA scan to detect VUR is 0.75 (CI: 0.67-0.81) with a specificity of 0.48 (CI: 0.38-0.57), and a negative DMSA scan resulting in a very low probability of high-grade VUR [507].

3.10.3.5.3 Voiding cystourethrography/urosonography

The optimum method to exclude or confirm VUR is VCUG. The timing of VCUG does not influence the presence or severity of VUR [508]. Performance of early VCUG in patients with proven sterile urine does not cause any significant morbidity [509]. Using harmonic voiding urosonography may be an alternative to the standard VCUG avoiding radiation [510]. Visulatisation of the urethra may be difficult with this technique.

It is important to diagnose high-grade VUR after the first UTI since this is an important risk for renal scarring. On the other hand, physicians want to avoid unnecessary VCUG investigations at the same time, given its invasive character and radiation burden [498, 511]. Various studies have investigated the risk factors for high-grade VUR and a top down approach is feasible. The most important risk factors for high-grade VUR and subsequent renal scarring are: abnormal renal US, high fever UTI and non-E. Coli infections. Different top down strategies with selective VCUG investigations have been proposed [512-516]. Based on these studies we recommend the following updated diagnostic strategy (see Figure 6).

Figure 6: Diagnosis strategy for first febrile UTI



UTI = urinary tract infection; VUR = vesicoureteral reflux; i.v. = intravenous; BBD = bladder and bowl dysfunction.

*3.10.4 **Management***

3.10.4.1 Administration route of antibacterial therapy

The choice between oral and parenteral therapy should be based on patient age; clinical suspicion of urosepsis; illness severity; refusal of fluids, food and/or oral medication; vomiting; diarrhoea; non-compliance; and complicated pyelonephritis (e.g. urinary obstruction). As a result of the increased incidence of urosepsis and severe pyelonephritis in newborns and infants aged less than two months, parenteral antibiotic therapy is recommended. Electrolyte disorders with life-threatening hyponatraemia and hyperkalaemia based on pseudohypoaldosteronism can occur in these cases [517, 518].

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 [481]. Not all available antibiotics are approved by national health authorities, especially in infancy. When recent urinary cultures are available use these sensitivity patterns in the choice for treatment. In children who require intravenuous treatment tobramycin or gentamicin is recommended if there is normal kidney function. When abnormal kidney function is suspected, ceftriaxon or cefotaxime are alternative treatment options. In children who can receive oral treatment without any known resistant urinary cultures, cefixime or amoxicillin-clavulanate are the empirical treatment options [519]. 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 [520-522]. Delaying treatment in children with a febrile UTI for more than 48-72 hours increases the risk of renal scars [463, 507].

3.10.4.2 Duration of therapy

Prompt adequate treatment of UTI can prevent the spread of infection and renal scarring. In newborns and young infants with a febrile UTI, up to 20% may have a positive blood culture [467, 472]. Children with bacteremia did not show significant clinical differences with non-bacteremic infants, but did receive longer parental treatment [523]. In late infancy, there are no differences between strategies regarding the incidence of parenchymal scars, as diagnosed with DMSA scan [524]. Outcomes of short courses (one to three days) are inferior to seven to fourteen-day courses [481]. However, a simple cystitis can be treated with three to five days of antibiotics [519]. No significant difference in recurrent UTIs and rehospitalisation was found between seven day parental treatment and longer regimens for bacteremic UTI in younger infants [525]. In young infants a short course of parental treatment with early conversion to oral antibiotics may be considered. The use of exclusively oral therapy with a third-generation cephalosporin (e.g. cefixime or ceftibuten) has been demonstrated to be equivalent to the usual two to four days intravenous therapy followed by oral treatment [526-529]. Similar data have been shown for amoxicillin-clavulanate [530]. 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 [531].

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 [472]. A temporary urinary diversion (transurethral catheter, suprapubic cystostomy, percutaneous nephrostomy or ureteral stenting) might be required in case of failure of conservative treatment in obstructive uropathy. Children with acute focal bacterial nephritis often present without pyyuria and significant bacteriuria. For the majority of children, the pathogenesis is related to ascending infection due to pre-existing uropathy, especially VUR or urinary obstruction. Initial management consists of broad-spectrum antibiotics with good tissue penetration. A treatment regimen of a total of three weeks with initial intravenous and subsequently oral therapy tailored to the pathogen identified in culture is recommended [532].

3.10.4.3 Antimicrobial agents

There is a great difference in the prevalence of antibiotic resistance of uropathogenic E. coli in different countries, with increased high resistance patterns in countries outside of the Organisation for Economic Co-operation and Development (OECD) [533]. There are upcoming reports of UTIs caused by extended spectrum ß-lactamase-producing enterobacteriaceae (ESBL) in children, with pooled numbers of UTI caused by ESBL producing bacteria of around 14% [534]. Within OECD countries the prevalence of resistance was 53% for ampicillin, 24% for trimethoprim, 8% for co-amoxiclav, 2% for ciproxin and 1% for nitrofurantoin [533]. Several risk factors and determinants for UTIs caused by ESBL and non-E. Coli bacteriae have been identified: history of infection, recent hospitalisation, short-term exposure to antiobiotics, and prophylaxis [533, 535, 536].Overall, oral nitrofurantoin seems to be a good empirical choice in the treatment of cystitis [537].

The choice of antibiotics should be guided by good antibiotic stewardship. It is important to be aware of the local resistance patterns. These are variable between countries and moreover between hospitals. Local antibiotic protocols and web-based recommendations can guide the choice for type of antibiotic therapy. The individual patient's previous urine cultures should also be taken into account in this decision. The daily dosage of antibiotics is depended on the age, weight of the child as well as on renal and liver function.

3.10.4.4 Preventative measures

Recurrent UTIs are problematic because the symptoms are bothersome to children and recurrent febrile UTIs will also result in renal scarring [465]. Therefore, it is important to prevent the incidence of recurrent UTIs.

3.10.4.4.1 Chemoprophylaxis

Chemoprophylaxis is commonly used to prevent UTIs in children. However, with the increasing bacterial resistance numbers, it should be carefully considered which patients should receive antibacterial prophylaxis. The evidence for the use of antibacterial prophylaxis has been conflicting. Its use causes a reduction of the

number of recurrent symptomatic UTIs, but long-term use of antibacterial prophylaxis has also been associated with increased microbial resistance [469, 538]. Its use did not reduce newly acquired renal damage in children with first or second UTI [538]. However, when used in patients with anatomic abnormalities of the urinary system a reduction in UTIs and subsequent renal scarring was shown [469, 538]. In children with BBD and VUR, a benefit was seen in the reduction of recurrent UTI with the use of antomicrobial prophylaxis [539, 540] (see also Chapter 3.15 on VUR). For the specific group of patients with incomplete bladder emptying with properly performed clean intermittent catheterisation but still suffering from recurrent UTIs the intravesical application of gentamycin has proven to be effective [541].

Table 1: Drugs for antibacterial prophylaxis*

Substance	Prophylactic dosage (mg/kg bw/d)	Limitations in neonates and infants
Trimethoprim**	2	Not recommended under 6 weeks of age
Trimethoprim Sulfamethoxazole	1-2 10-15	Not recommended under two months of age
Sulfamethoxazole	1-2	Until three months of age
Nitrofurantoin**	1-2	Not recommended under two months of age
Cefaclor	10	No age limitations
Cefixim	2	Preterms and newborns

* *Reproduced with permission from the International Consultation on Urological Diseases (ICUD), International Consultation on Urogenital Infections, 2009. Copyright© by the European Association of Urology [542].*

** *Substances of first choice are nitrofurantoin and trimethoprim. In exceptional cases, oral cephalosporin can be used.*

3.10.4.4.2 Dietary supplements

Cranberry, mostly as juice, has been shown to prevent UTIs in healthy children, while in children with urogenital abnormalities, cranberries appear to be just as effective as antibiotic prophylaxis [543]. The results for probiotics are somewhat more conflicting, with one systematic review not ruling out any effect [335] and a RCT showing promising results in children with normal urogenital anatomy [544]. A meta-analysis could not demonstrate a beneficial effect, only as an adjuvant to antibiotic prophylaxis [545].

Other supplements of interest were Vitamin A, which showed promising results in preventing renal scarring in children with acute pyelonephritis [546, 547]. The use of Vitamin E could possibly improve the symptoms of UTI [548]. More studies into these supplements are warranted.

3.10.4.4.3 Preputium

A risk reduction of recurrent UTI regarding the preputium has been shown in two studies. When a physiologic phimosis is present in boys with a UTI the use of steroid cream significantly reduced recurrent UTIs [41]. In boys with recurrent UTIs and hydronephrosis present, ten boys would need to be circumcised to prevent one UTI [39].

3.10.4.4.4 Bladder and bowel dysfunction

Bladder and bowel dysfunction is a risk factor for which each child with UTI should be screened upon presentation [460]. Normalisation of micturition disorders or bladder overactivity 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 [540]. Treatment of constipation leads to a decrease in UTI recurrence and a multidisciplinary approach is recommended [460, 539, 540]. Therefore, exclusion of BBD is strongly recommended in any toilet-trained child with febrile and/or recurrent UTI, and it should be treated (For treatment see chapter 3.11 on LUTS).

3.10.4.5 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. Repeated 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 [549]. A cut-off value of serum procalcitonin of 1.0 ng/mL has been shown to be predictive of acute

pyelonephritis in young children [550]. In patients with febrile UTI, serum electrolytes and blood cell counts should be followed up.

*3.10.5 **Summary of evidence and recommendations for the management of UTI in children***

Summary of evidence	LE
Urinary tract infection represents the most common bacterial infection in children less than 2 years of age. The incidence varies depending on age and sex.	1b
Classifications are made according to the site, episode, severity, symptoms and complicating factors. For acute treatment, site and severity are most important.	2b
The number of colony forming units (cfu) in the urine culture can vary, however, any colony count of one specimen indicates a high suspicion for UTI.	2b
Due to increasing resistance numbers good antibiotic stewardship should guide the choice of antibiotics, taking into account local resistance patterns, old urine cultures (when available) and clinical parameters.	2a
Preventive measures against recurrent UTIs include: chemoprophylaxis (oral and intravesical), cranberries, probiotics and Vitamin A and E.	2a
Urinalysis by dipstick yields rapid results, but it should be used with caution. Microscopic investigation is the standard method of assessing pyuria after centrifugation.	2a
During acute UTI both DMSA and diffusion-weighted MRI can confirm pyelonephritis or parenchymal damage.	2a

Recommendations	LE	Strength rating
Take a medical history, assess clinical signs and symptoms and perform a physical examination to diagnose children suspected of having a urinary tract infection (UTI).	3	Strong
Exclude bladder- and bowel dysfunction in any toilet-trained child with febrile and/or recurrent UTI.	3	Strong
Clean catch urine can be used for screening for UTI. Bladder catheterisation and suprapubic bladder aspiration to collect urine can be used for urine cultures.	2a	Strong
Do not use plastic bags for urine sampling in non-toilet-trained children since it has a high risk of false-positive results.	2a	Strong
Midstream urine is an acceptable technique for toilet-trained children.	2a	Strong
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	Strong
Treat febrile UTIs with four to seven day courses of oral or parenteral therapy.	1b	Strong
Treat complicated febrile UTI with broad-spectrum antibiotics.	1b	Strong
Offer long-term antibacterial prophylaxis in case of high susceptibility to UTI and risk of acquired renal damage and lower urinary tract symptoms.	1b	Strong
In selected cases consider dietery supplements as an alternative or add-on preventive measure.	2a	Strong
In infants with febrile UTI use renal and bladder ultrasound to exclude obstruction of the upper and lower urinary tract within 24 hours.	2a	Strong
In infants, exclude vesicoureteric reflux (VUR) after first epidose of febrile UTI with a non-E. Coli infection. In children more than one year of age with an E. Coli infection, exclude VUR after the second febrile UTI.	2a	Strong

3.11 Day-time lower urinary tract conditions

*3.11.1 **Terminology, classification, epidemiology and pathophysiology***

Urinary incontinence in children may be caused by congenital anatomical or neurologic abnormalities such as ectopic ureter, bladder exstrophy or myelomeningocele (MMC). In many children, however, there is no such obvious cause for the incontinence, and they are referred as having functional bladder problems. The most recent International Children's Continence Society (ICCS) document suggests using the term day-time lower urinary tract (LUT) conditions to group together all functional bladder problems in children.

Normal storage and emptying of the bladder at a socially accepted place and time is mostly achieved by age three to four. Children with LUT conditions would present with failure to achieve continence (being still wet after the age of four), urgency, weak stream, hesitancy, frequency and accompanied UTIs. Isolated night-time wetting without any day-time symptoms is known as 'enuresis' and considered as a different entity [551].

As different studies have used varying definitions and criteria, it is difficult to give reliable percentages regarding the incidence of this problem. Reported prevalence ranges widely from 1% to 20% [552-560]. Due to increasing awareness and better access to specialised health care, the prevalence seems to be increasing [561, 562].

Lower urinary tract conditions in children may be due to disturbances of the filling phase, the voiding phase or a combination of both in varying severity. Mainly the conditions are divided into either overactive bladder (OAB) or dysfunctional voiding. They can, of course, coincide and one may even be causative of the other. Dysfunctional bowel emptying may also be part of the clinical problems and BBD is the term used to cover concomitant bladder and bowel disturbances.

Lower urinary tract conditions are considered to be the result of incomplete or delayed maturation of the bladder sphincter complex. The pons is considered to be responsible for detrusor sphincter co-ordination while the cortical area is responsible for inhibition of the micturition reflex and voluntary initiation of micturition. Therefore overactivity would be the result of delayed maturation of cortical control, while dysfunctional voiding would be the result of non-maturation of the co-ordination. Detrusor overactivity should not be considered as a sole bladder based problem but more a symptom of a centrally located dysfunction affecting bladder, bowel and even mood and behaviour [563].

A link between LUT and behavioural disorders such as ADHD (attention deficit/ hyperactivity disorder) has also been shown [564-566].

3.11.1.1 Filling-phase (storage) dysfunctions

In filling-phase dysfunctions, the detrusor can be overactive, as in OAB, or underactive, as in underactive bladder (UAB). Overactivity of the bladder is the most common problem, seen mostly around five to seven years of age. This may lead to disturbances characterised by urgency, frequency and at times urgency incontinence. Some children habitually postpone micturition leading to voiding postponement. Therefore, holding manoeuvres such as leg crossing and squatting can often be seen in this group. Recurrent UTIs are common and high-pressure state of the bladder can be a cause of VUR. Constipation can be an additional aetiological factor, which needs to be assessed. In children with an underactive detrusor, voiding occurs with reduced or minimal detrusor contractions with post-void residuals. Urinary tract infections, straining to void, constipation and incontinence is common. Incontinence often occurs when the bladder is over-distended in the form of overflow incontinence.

3.11.1.2 Voiding-phase (emptying) dysfunctions

In voiding-phase (emptying), incomplete relaxation or tightening of the sphincteric mechanism and pelvic floor muscles results in staccato voiding pattern (continuous urine flow with periodic reductions in flow rate precipitated by bursts of pelvic floor activity) or an interrupted voiding pattern (unsustained detrusor contractions resulting in infrequent and incomplete voiding, with micturition in fractions). The general term for this condition is dysfunctional voiding and is associated with elevated bladder pressures and PVRs. Symptoms will vary depending on the severity of inco-ordination between bladder and the sphincter. Staccato voiding is in less severe forms and interrupted voiding and straining is in more severe forms. The co-existence of constipation and LUTD and recurrent UTI is well described [567]. There is no evidence to conclude if bladder problems or bowel problems are the leading cause. The prevalence of constipation in older children varies from 5 to 27%. Approximately 90% of them being functional constipation without an organic cause In children with functinal constipation the prevelance of bladder symptoms have been shown to be as high as 64% [568, 569].

In incomplete emptying, high voiding pressures generated by bladder working against a functional obstruction caused by non-relaxing sphincter may induce not only UTIs but also VUR. It is been shown that LUTD is more significant for the occurrence of UTI than VUR itself [570]. In the majority of children with dysfunctional voiding the recurrent infections disappear following successful treatment, which confirms the hypothesis that dysfunctional voiding is the main factor responsible for the infections. Spontaneous resolution of VUR may also be seen after successful treatment of dysfunctional voiding.

3.11.2 ***Diagnostic evaluation***

The evaluation of LUT conditions includes medical and voiding history (bladder diaries and structured

questionnaires), a physical examination, a urinalysis, and uroflowmetry with PVR. The upper urinary tract (UUT) needs to be evaluated in children with recurrent infections and dysfunctional voiding. Uroflowmetry can be combined with pelvic floor electromyography to demonstrate overactivity of the pelvic floor muscles during voiding. Urodynamic studies are usually reserved for patients with therapy resistant dysfunctional voiding and those not responding to treatment who are being considered for invasive treatment [566, 571-574].

In addition to a comprehensive medical history a detailed voiding diary provides documentation of voiding and defecation habits, frequency of micturition, voided volumes, night-time urine output, number and timing of incontinence episodes, and fluid intake. A voiding diary should at least be done for two days, although longer observation periods are preferred. A voiding diary provides information about storage function and incontinence frequency, while a pad test can help to quantify the urine loss. In the paediatric age group, where the history is taken from both the caregivers 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 caregivers and should be specifically requested, using the questionnaire as a checklist. Some symptom scorings have been developed and validated [575, 576]. Although the reliability of questionnaires are limited they are practical in a clinical setting to check the presence of symptoms and have also been shown to be reliable to monitor the response to treatment. History taking should also include assessment of bowel function. For evaluation of bowel function in children, the Bristol Stool Scale is an easy-to-use tool [577, 578].

Urinalysis and urinary culture are essential to evaluate for UTI. Since transient voiding symptoms are common in the presence of UTI, exclusion of UTI is essential before further management of symptoms. During clinical examination, genital inspection and observation of the lumbosacral spine and the lower extremities are necessary to exclude obvious uropathy and neuropathy.

Uroflowmetry with PVR evaluates the emptying ability, while an UUT US screens for (secondary) anatomical changes. A flow rate which reaches its maximum quickly and levels off ('tower shape') may be indicative of over-active bladder whereas interrupted or staccato voiding patterns may be seen in dysfunctional voiding. Plateau uroflowmetry patterns are usually seen in anatomic obstruction of flow. A single uroflowmetry test may not always be representative of the clinical situation and multiple uroflowmetry tests, which all give a similar result, are more reliable. Uroflowmetry examination should be done when there is desire to empty the bladder and the voided volume should at least be 50% of the age-expected capacity [(age in years) + 1] x 30 mL for the children. While testing the child in a clinical environment, the impact of stress and mood changes on bladder function should also be taken into account [579, 580].

In the case of treatment failure re-evaluation is warranted and (video)-urodynamic (VUD) studies and neurological evaluation 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 [581] (LE: 1b).

Video-urodynamics may also be used as initial investigational tool in patients with suspicion of reflux. In this case reflux may be observed along with bladder dynamics. In the case of anatomical problems, such as posterior urethral valve (PUV) problems, syringocoeles, congenital obstructive posterior urethral membrane (COPUM) or Moormann's ring, it may be necessary to perform 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.

3.11.3 ***Management***

The treatment of LUTD involves a multimodal approach, involving strategies such as behavioural modification, and anticholinergic medication along with underlying and potentially complicating conditions such as constipation and UTIs.

Behavioural modification, mostly referred to as urotherapy, is a term which covers all non-pharmacological and non-surgical treatment modalities. It includes standardisation of fluid intake, bowel management; timed voiding and basic relaxed voiding education. The child and family are educated about normal bladder function and responses to urgency. Voiding regimens are instituted and UTIs and any constipation are treated. Treatment is aimed at optimising bladder emptying and inducing full relaxation of the urinary sphincter or pelvic floor prior to and during voiding.

Strategies to achieve these goals include:

1. Information and demystification, which includes explanation about normal LUT function and how a particular child deviates from normal function.
2. Instructions about what to do about the problem:

- Regular voiding habits, sound voiding posture, pelvic floor awareness and training to relax pelvic floor and avoiding holding manoeuvres.
- 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.

Recurrent UTIs and constipation should also be treated and prevented during the treatment period. In case of combined BBD it is advised to treat the bowel dysfunction first [561] as LUTS may disappear after successful management of bowel dysfunction.

Addition of other strategies, as below, may be needed:
- Pelvic floor muscle awareness practices with repeated sessions of biofeedback visualisation of uroflow curves and/or pelvic floor activity and relaxation.
- Clean intermittent self-catheterisation for large PVR volumes of urine.
- Antimuscarinic drug therapy if detrusor overactivity is present.
- If the bladder neck is associated with increased resistance to voiding, α-blocker drugs may be introduced.

Treatment efficacy can be evaluated by improvement in bladder emptying and resolution of associated symptoms. Controlled studies of the various interventions are needed. As with detrusor overactivity, the natural history of untreated dysfunctional voiding is not well delineated and optimum duration of therapy is poorly described. A high success rate 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 [582]. A Cochrane analysis found very little evidence that can help to make evidene-based treatment decisions [583].

3.11.3.1 Specific interventions

As well as urotherapy, there are some specific interventions, including physiotherapy (e.g. pelvic floor exercises), biofeedback, alarm therapy and neuromodulation. Although good results with these treatment modalities have been reported, the level of evidence remains low, since only a few RCTs were published [584-590].

A systematic review reports that biofeedback is an effective, non-invasive method of treating dysfunctional voiding, and approximately 80% of children benefited from this treatment. However, most reports were of low level of evidence and studies of more solid design such as RCTs should be conducted [591]. A more recently published multicentre controlled trial of cognitive treatment, placebo, oxybutynin and bladder and pelvic floor training did not report better results with oxybutynin and pelvic floor training compared to standard urotherapy [581] (LE: 1b).

Two RCTs on underactive bladder without neurophatic disease have been published. Transcutaneous interferential electrical stimulation and animated biofeedback with pelvic floor exercise have been shown to be effective [592, 593]. In some cases, pharmacotherapy may be added. Some studies on orthosympathicomimetics have been published with a low level of evidence [594].

Overactive bladder is common in the paediatric population. Although a stepwise approach starting with behavioural therapy is advised, antimuscarinic agents remain the mainstay of medical treatment for OAB. Oxybutynin is the most commonly used antimuscarinic in the paediatric population. The response to antimuscarinics varies and many children experience serious side effects. Although there have been reports about the use of tolterodine, fesoterodine, trospium, propiverine, and solifenacin in children, to date, most of them are off-label depending on age and national regulations. A few RCTs have been published, one on tolterodine showed safety but not efficacy [595], while another on propiverine showed both safety and efficacy [596]. The study on solifenacin showed its efficacy with side effects like constipation and electrocardiogram changes [597].

The difference in results is probably due to study design. Despite the low level of evidence for the use of anticholinergics and antimuscarinics, their use is recommended because of the large number of studies reporting a positive effect on OAB symptoms. Although α-blocking agents are used occasionally, an RCT showed no benefit [598]. Botulinum toxin injection seems promising, but can only be used off-label [599].

A meta-analysis reports that neuromodulation therapy may lead to better partial improvement of nonneurogenic OAB; however, it may not render a definitive complete response. Office-based neuromodulation seems more efficacious than self-administered neuromodulation [600]. These new treatment modalities can only be

recommended for standard therapy-resistant cases [601]. Despite early successful treatment, there is evidence that there is a high recurrence rate of symptoms in the long term which necessitates long-term follow-up [602]. In addition, many patients may present later in adulthood with different forms of LUTD [603].

3.11.4 Summary of evidence and recommendations for the management of day-time lower urinary tract conditions

Summary of evidence	LE
The term 'bladder bowel dysfunction' should be used rather than 'dysfunctional elimination syndrome and voiding dysfunction'.	4
Day-time LUTS has a high prevalence (1% to 20%).	2

Recommendations	LE	Strength rating
Use two day voiding diaries and/or structured questionnaires for objective evaluation of symptoms, voiding drinking habits and response to treatment.	2	Strong
Use a stepwise approach, starting with the least invasive treatment in managing day-time lower urinary tract dysfunction in children.	4	Weak
Initially offer urotherapy involving bladder rehabilitation and bowel management.	2	Weak
If bladder bowel dysfunction is present, treat bowel dysfunction first, before treating the lower urinary tract condition.	2	Weak
Use pharmacotherapy (mainly antispasmodics and anticholinergics) as second line therapy in overactive bladder.	1	Strong
Use antibiotic prophylaxis if there are recurrent infections.	2	Weak
Re-evaluate in case of treatment failure; this may consist of (video) urodynamics MRI of lumbosacral spine and other diagnostic modalities, guiding to off-label treatment which should only be offered in highly experienced centres.	3	Weak

3.12 Monosymptomatic nocturnal enuresis – bedwetting

3.12.1 Epidemiology, aetiology and pathophysiology

Monosymptomatic nocturnal enuresis (NE), also known as bedwetting, is defined as an intermittent nocturnal incontinence. It is a relatively frequent symptom in children, 5-10% at seven years of age and 1–2% in adolescents. There is a gender difference in the incidence: two boys to one girl at any age [604]. With a spontaneous yearly resolution rate of 15% (at any age), it is considered as a relatively benign condition [579, 605]. Seven out of 100 seven-year-old bedwetting children will continue to wet their bed into adulthood. Nocturnal enuresis is considered primary when a child has not yet had a prolonged period of being dry (six months). The term "secondary NE" is used when a child or adult begins wetting again after having stayed dry.
Non-monosymptomatic NE is defined as the condition of NE in association with day-time lower urinary tracts symptoms (LUTS, recurrent UTIs and/or bowel dysfunction) [605, 606]. The presence of constipation has a negative association with bladder capacity [607].

Nocturnal enuresis has significant secondary stressful, emotional and social consequences for the child and their caregivers. A lower quality of life has been reported for children with NE compared to controls and NE can influence relationships with friends and family [608-611]. Therefore, treatment is advised from the age of six to seven years onwards considering mental status, family expectations, social issues, and cultural background.

There is a clear hereditary factor in NE. If none of the parents or their immediate relatives has suffered from bedwetting, the child has a 15% chance of wetting its bed. If one of the parents, or their immediate relatives have suffered from bedwetting, the chance of bedwetting increases to 44%, and if both parents have a positive history the chance increases to 77%. However, from a genetic point of view, enuresis is a complex and heterogeneous disorder. Loci have been described on chromosomes 12, 13 and 22 [606].

Children with NE are considered deep but poor sleepers due to high arousal thresholds and frequently disturbed sleep. High arousal threshold is the most important pathophysiological factor in the aetiology of NE: the child does not wake up when the bladder is full. Full night polysomnographic recordings support this hypothesis by demonstrating the disruption of children's sleep microstructure [612]. In addition to the high arousal threshold, there needs to be an imbalance between night-time urine output and night-time bladder capacity [579, 605, 606]. Recently, attention has been given to the chronobiology of micturition in which the existence of a circadian clock in kidney, brain and bladder is postulated [613].

A high incidence of comorbidity and correlation between nocturnal urine production and sleep disordered breathing, such as obstructive sleep apnoea, has been found and investigated [614]. Symptoms such as habitual snoring, apnoeas, excessive sweating at night and mouth breathing in the patient history or via sleep questionnaires, such as the BEARS questionnaire [615], can lead to the detection of sleep disorders and/or adenotonsillar hypertrophy. When present, a consultation with the ENT specialist can be considered [616].
Obesity is associated with a higher incidence of NE and a lower efficacy for treatment [617]. The presence of allergic diseases has been recognised as a risk factor of NE and with a greater risk for more allergic episodes [618-620].

It is important to consider the child's and family's psychological status as primary NE has been associated with psychopathology, such as Attention Deficit Hyperactivity Disorder (ADHD) and depressive symptoms [621, 622]. In children with ADHD symptoms of NE are more severe and it is important to inform the child and the parents about a delayed success rate and higher relapse rate compared to children without ADHD [623].

*3.12.2 **Diagnostic evaluation***

The diagnosis is mainly obtained by history-taking. Focused questions to differentiate monosymptomatic vs. non-monosymptomatic, primary vs. secondary, comorbid factors such as behavioural or psychological problems and sleep disorder breathing, should be asked. In addition, a two-day complete micturition and drinking diary, which records day-time bladder function and drinking habits will further exclude comorbid factors such as LUTS and polydipsia.

Specific attention should be made regarding bowel movements as irregular bowel movements can change the diagnosis from monosymptomatic NE to non-monosymptomatic NE. If constipation or faecal incontinence is found (it is reported in up to 20% of children with NE), it should be treated simultaneously, and the family should be informed that constipation can negatively influence treatment outcomes [624, 625].

The night-time urine production should be registered by weighing the night-time diapers in the morning and adding the first morning voided volume [626]. The night-time urine production should be recorded over (at least) a two-week period to diagnose an eventual differentiation between a high night-time production (more than 130% of the age expected bladder capacity) vs. a night-time OAB.

A physical examination should be performed with special attention to the back of the child (to exclude any neurological problem), the external genitalia and surrounding skin, as well as to the condition of the clothes (wet underwear or encopresis).

Urine analysis is indicated if there is a sudden onset of bedwetting, a suspicion or history of UTIs, or inexplicable polydipsia.

A uroflowmetry and US is indicated only if there is a history of previous urethral or bladder surgery and presence of daytime urinary symptoms. For further evaluation, see Section 3.10 on Day-time LUT conditions.

There is no clinical indication nor use for a functional MRI (fMRI) in the diagnostic of NE. Research is ongoing, however one of the main issues is the fact that the MRI is performed in an awake state, whereas the NE is a solely event during sleep. The use of fMRI in the elucidation of the NE's neuropathological mechanisms has not yet been fruitful [627, 628].

*3.12.3 **Management***

Before introducing any form of possible treatment, it is of utmost importance to explain the bedwetting condition to the child and the caregivers in order to demystify the problem. Parents should be encouraged to seek medical attention for their bedwetting children and be informed that it is known that the quality of life of parents with a child with NE is negatively impaired. Medical providers assisting families with a child must be aware of this fact and therefore guide parents, by explaining that the key role for treating a child with NE is the ability to understand and the co-operation of the child itself [629].

Since the COVID-19 pandemic situation and promotion of virtual contacts between doctors and patients, it has been shown that telemedicine is a good method of closely follow-up and can be used for follow-up after treatment [630].

3.12.3.1 Supportive treatment measures

Initially, supportive measures including normal and regular 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, also called as basic bladder advice, has not been shown to be successful in the early treatment of NE [631]. To assure good sleep quality, specifically in children with NE, it is also recommended to limit the use of electronic devices before bedtime [632].

Referral for psychological support should be advised and followed-up for patients with NE and their families, especially if the NE comorbid factor is developmental, attention or learning difficulties, family problems, parental distress and possible punishment of the child are observed. Parental stress levels are higher compared to parents of non-NE children [633] and anger is found to be the most common parental reaction towards NE children [634], this would explain why childhood traumas such as neglect and abuse are more often seen in children with NE [635]. Psychological interventions with parents of NE children were shown to significantly improve their coping mechanisms [636].

3.12.3.2 Wetting alarm treatment

The nocturnal alarm treatment relies on the use of a device that is activated by getting wet. The goal of this therapeutic approach is that the child wakes up by the alarm, which can be acoustic or tactile, either by itself or with the help of a caregiver. Their method of action is to repeat the awakening and therefore change the high arousal to a low arousal threshold, specifically when a status of full bladder is reached. In the most recent Cochrane review (even though the quality of the included studies was low), several studies have shown that alarm treatment will reduce the number of wet nights a week. An alarm treatment has a higher complete response rate and a low relapse rate compared to no treatment at all [637]. In the event of relapse after initial success, one should actively investigate for OAB [638]. The recommended length of therapy with the alarm treatment continues to be uncertain, varying from 8-12 weeks (ICCS) to 16-20 weeks [639].

Regular follow-up will improve the success. It is of utmost importance that the child plays an active role in the alarm treatment, is willing to continue and understand the purpose of the treatment modality.

3.12.3.3 Medical treatment

If the child and the family would like to act on the high night-time urine production and eventual night-time OAB, they should be able and willing to adjust their drinking habits and take either desmopressin or a combination of desmopressin and an anticholinergic drug.

Success rates of 70% can be obtained with Desmopressin , either as tablets (200-400 µg), or as sublingual Desmopressin oral lyophilisate (120-240 µg). A rare side-effect is water intoxication which can be prevented by adequate water intake. The dosage of 120 ug has been shown to be effective and safe [640]. A structured titration increase up to 240 ug has been shown to be effective [641]. Predictive factors for success with Desmopressin have been identified: older children, in children with fewer wet nights and high night-time urine production [642]. Children that show a good response on low-dose Desmopressin are more likely to show a complete response during the maintenance period [643]. When poor responses are seen on Desmopressin be aware of low compliance [644]. Relapse rates can be high after Desmopressin discontinuation [579], it is unclear if structured withdrawal will result in lower relapse rates [645, 646]. A nasal spray is no longer recommended due to the increased risk of overdose [647].

In the event of Desmopressin-resistant treatment for NE or if a suspicion exists for night-time OAB, combination of Desmopressin with anticholinergics is safe and efficient, even after cessation of treatment [648-651]. With night-time OAB a treatment failure to Desmopressin can be explained because of the bladder reservoir dysfunction [652]. There is no indication for monotherapy with an anticholinergic drug [653].

Alarm and Desmopressin treatment have comparable efficacy in achieving >50% reduction in wet nights. Alarms offer superior treatment response (OR: 2.89, 95% CI 1.38 to 6.04) and lower relapse rates (OR: 0.25, 95% CI 0.12 to 0.50) in children [654]. Multimodal treatment can achieve a partial or full response in 80% of children. However, side effects are seen in up to 30% of children [655].

3.12.3.4 Electrical neuromodulation

Several systematic reviews and randomized trials have documented potential benefits of electrical neural stimulation for NE. However, the quality of the included studies was low and different types of electrical neural stimulation, such as intra-anal stimulation and interferential current stimulation have been included [656-659]. The one RCT that compares transcutaneous electrical nerve stimulation to placebo demonstrates no anti-enuretic effect [660].

3.12.3.5 Complementary treatments:

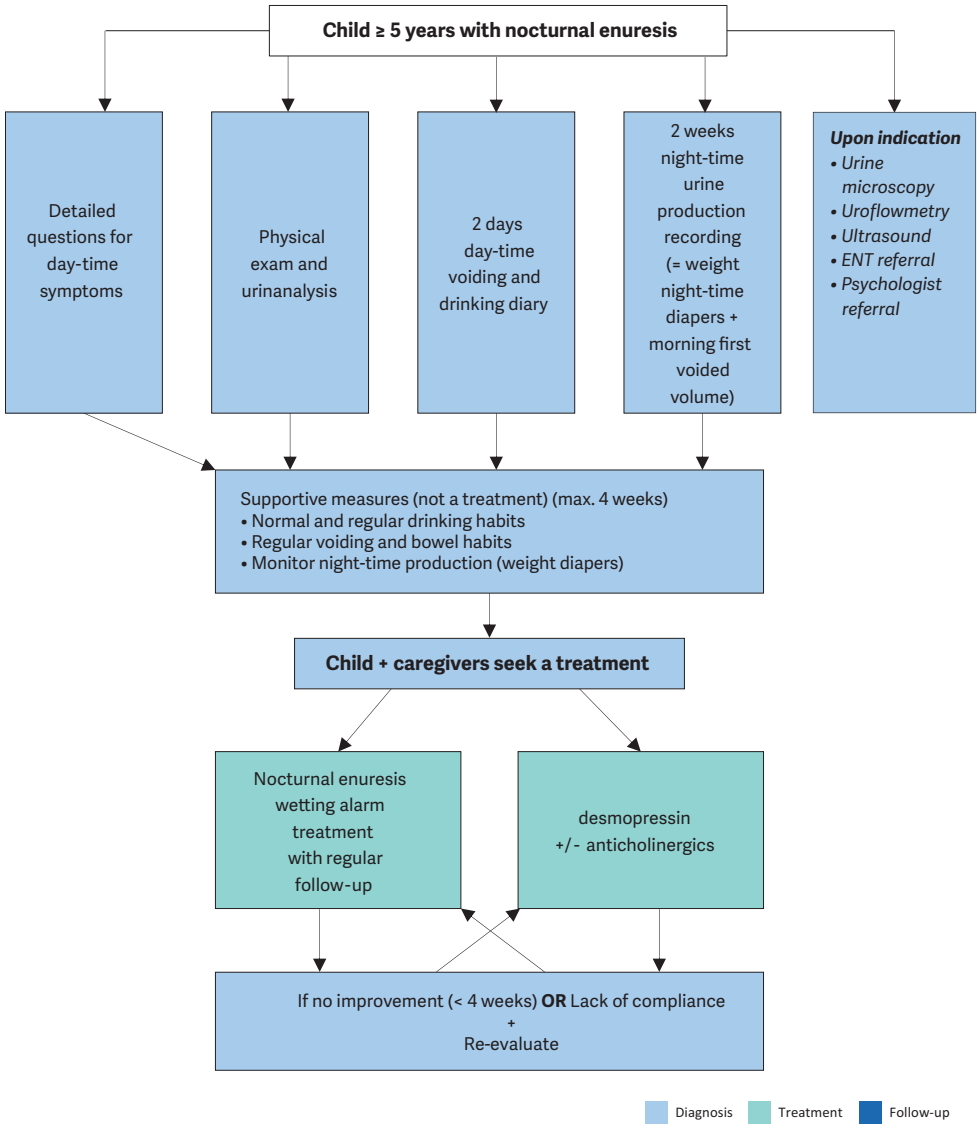
A Cochrane review showed no benefit for treatments such as hypnosis, psychotherapy, acupuncture, chiropractic and medicinal herbs for the treatment of NE [661].

3.12.3.6 Conservative "wait and see" approach

If the child and its family is unable to comply with a treatment, if the treatment options are not possible for the

family situation, and if there is no social pressure, a "wait and see" approach can be chosen. However, in this approach, it is important to emphasise the fact that the child should wear diapers at night to ensure a normal quality of sleep [662]. The success rate of wait and see is 15% per year, independent of age. Figure 6 presents stepwise assessment and management options for NE.

Figure 7: A stepwise assessment and management options for NE



ENT = ear, nose and throat.

3.12.4 *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	Strength rating
Do not treat children less than five years of age in whom spontaneous cure is likely, but inform the family about the involuntary nature, the high incidence of spontaneous resolution and the fact that punishment will not help to improve the condition.	2	Strong

Use micturition diaries or questionnaires to exclude day-time symptoms.	2	Strong
Perform a urine test to exclude the presence of infection or potential causes such as diabetes insipidus.	2	Strong
Offer supportive measures in conjunction with other treatment modalities, of which pharmacological and alarm treatment are the two most important.	1	Strong
Offer desmopressin in proven night-time polyuria.	1	Strong
Offer alarm treatment in motivated and compliant families.	1	Strong

3.13 Management of neurogenic bladder

*3.13.1 **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 ultimately to renal scarring and renal failure requiring dialysis and/or transplantation. Conservative treatment starting in the first year of life is the first choice, however, surgery may be required at a later stage to establish adequate bladder storage, continence and drainage later on [663]. The main goals of treatment concerning the urinary tract are prevention of UTI's, urinary tract deterioration, achievement of continence at an appropriate age and promoting as good as possible QoL [4, 5]. With regard to the associated bowel dysfunction, stool continence, with evacuation at a social acceptable moment, is another goal as well as education and treatment of disturbance in sexual function. Due to the increased risk of development of latex allergy, latex-free products (e.g., gloves, catheters etc.) should be used from the very beginning whenever possible [664].

Neurogenic bladder in children with myelodysplasia presents with various patterns of Detrusor-Sphincter-Dyssynergia with a wide range of severity [665]. About 12% of neonates with myelodysplasia have no signs of neuro-urological dysfunction at birth [666]. Newborns with myelodysplasia who initially have normal urodynamic studies are at risk for neurological deterioration secondary to spinal cord tethering, especially during the first six years of life. Close follow-up of these children is important for the early diagnosis and timely surgical correction of tethered spinal cord, and for the prevention of progressive urinary tract deterioration [666]. At birth, the majority of patients have normal UUTs, but up to 60% develop upper tract deterioration due to bladder changes, UTI and /or VUR, if not treated properly [667-670]. Even today in a contemporary series around 50% of the patients are incontinent and 15% have an impaired renal function at the age of 29 years [671]. A systematic review concerning the outcome of adult meningomyelocele patients demonstrated that around 37% (8-85%) are continent, 25% have some degree of renal damage and 1.3% end stage renal failure [672]. The term "continence" is used differently in the reports, and the definition of "always dry" was used in only a quarter of the reports [673]. A nationwide survey in USA showed, that less than 50% of the adult spina population reported being continent [674], which demonstrates the need for better consulting and lifelong support.

The most common presentation at birth is myelodysplasia. The incidence of neural tube defects in Europe is 9.1 per 10,000 births and has not decreased in recent years, despite longstanding recommendations concerning folic acid supplementations [675]. The term myelodysplasia includes a group of developmental anomalies that result from defects in neural tube closure. Lesions include spina bifida aperta and occulta, meningocele, lipomyelomeningocele, or myelomeningocele. Myelomeningocele is by far the most common defect seen and the most detrimental.

With antenatal screening spina bifida can be diagnosed before birth with the possibility of intrauterine closure of the defect [676, 677]. Traumatic and neoplastic spinal lesions of the cord are less frequent in children but can also cause severe urological problems. Other congenital malformations or acquired diseases can cause a neurogenic bladder, such as total or partial sacral agenesis which can be part of the caudal regression syndrome [678]. In any child presenting with anorectal malformation (ARM) and cloacal malformations, the development of a neurogenic bladder is possible [679]. 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. Finally, "non-neurogenic neurogenic" bladder dysfunction, such as Hinman or Ochoa syndrome, have been described, in which no neurogenic anomaly can be found, but severe bladder dysfunction as seen in neurogenic bladders is present [680, 681].

*3.13.2 **Classification systems***

As bladder sphincter dysfunction is poorly correlated with the type and spinal level of the neurological lesion, urodynamic and functional classifications are much more practical for defining LUT pathology and planning treatment in children.

The bladder and sphincter are two units working in harmony to act as a single functional unit. In patients with a neurogenic disorder, the storage and emptying phase of the bladder function can be disturbed. The bladder and sphincter may be either overactive or underactive and present in four different combinations. This classification system is based on urodynamic findings [682-684]:

- Overactive sphincter and overactive bladder.
- Overactive sphincter and underactive bladder.
- Underactive sphincter and overactive bladder.
- Underactive sphincter and underactive bladder.

*3.13.3 **Diagnostic evaluation***

Today several guidelines and timetables are used [685-687]. The Panel advocate proactive management in children with spinal dysraphism. In those with a safe bladder during the first urodynamic investigation, the next urodynamic investigation can be delayed until one year of age [4].

3.13.3.1 History and clinical evaluation

History should include questions on clean intermittent catheterisation (CIC) frequency, urine leakage, bladder capacity, UTI, medication, bowel function as well as changes in neurological status. A thorough clinical evaluation is mandatory including the external genitalia and the back. A two-day diary, recording drinking volume and times as well as CIC intervals, bladder volume and leakage can provide additional information about the efficacy of the treatment.

3.13.3.2 Laboratory and urinalysis

After the first week of life, plasma creatinine level should be obtained, later in life; cystatin level is more accurate [688, 689]. If there is any sign of decreased renal function, physicians should be encouraged to optimize the treatment as much as possible. The criteria for urine analysis are the same as for UTI (refer to Chapter 3.10). However, it is much easier for caregivers or patients to obtain catheter urine in patients who are on CIC. They can also perform a dip stick analysis to screen for UTI at home. (For relevance see Section 3.12.4.5). Albuminuria is an early marker of renal disease also in children with neurogenic bladder [690].

3.13.3.3 Ultrasound

At birth, US of the kidneys and bladder should be performed and then repeated at least annually. If there are any clinical changes in between, another US should be performed. Dilatation of the UUT should be reported according to the classification system of the Society of Foetal Urology [691], including the measurement of caliceal dilatation and anterior posterior diameter of the renal pelvis. Residual urine and bladder wall thickness should also be noted. A dilated ureter behind the bladder should be recorded. Bladder wall thickness has been shown not to be predictive of high pressures in the bladder during voiding and storage and cannot be used as a non-invasive tool to judge the risk for the UUT [692].

3.13.3.4 Urodynamic studies/videourodynamic

Urodynamic studies (UD) are one of the most important diagnostic tools in patients with neurogenic bladders. In newborns with spina bifida aperta), the first UD should be performed after the phase of spinal shock after closure, usually between the second and third months of life [693]. Especially in newborns, performing and interpretation of UD may be difficult, as no normal values exist. After that it should be repeated annually, depending on the clinical situation. During and after puberty bladder capacity, maximum detrusor pressure and detrusor leak point pressure increase significantly [694]. Therefore, during this time, a careful follow-up is mandatory.

3.13.3.4.1 Preparation before urodynamic studies

Before any UD a urine analysis should be undertaken. The first assessment should be done under antibiotic prophylaxis. A Cochrane analysis of nine randomised controlled trials showed, that the administration of prophylactic antibiotics compared to placebo reduced the risk of significant bacteriuria from 12% to 4% after UD studies. However, this was without significant difference for symptomatic UTI (20% vs. 28%), fever or discomfort [695]. If there is significant bacteriuria, antibacterial treatment should be discussed; especially in older patients a single dose may be sufficient [696].

Generally, UD-parameters should include:

- the cystometric capacity;
- the intravesical filling pressure;
- detrusor compliance;
- the intravesical pressure at the moment of voiding or leakage;

- the presence or absence of detrusor overactivity;
- the competence of the internal and external sphincter;
- the degree of synergy of the detrusor and sphincter during voiding;
- the PVR volume.

In infants, information on detrusor filling pressure and the pressure and bladder volume at which the child voids or leaks can be obtained [693]. Detrusor leak point pressure is more accurate than abdominal leak point pressure but keeping the rectal probe in an infant in place can be challenging [693]. Addition of fluoroscopy (video-urodynamic study) will provide information about presence of VUR, at what pressures VUR occurs and the configuration of the bladder neck during filling and leakage or voiding.

3.13.3.4.2 Uroflowmetry

Unlike in children with non-neurogenic voiding dysfunction, uroflowmetry can rarely be used since most affected patients do not void spontaneously. In those with cerebral palsy, non-neurogenic-neurogenic bladder or other neurological conditions allowing active voiding it may be a practical tool. It provides an objective way of assessing the efficiency of voiding, while recording of pelvic floor activity with electromyography (EMG) can be used to evaluate synergy between detrusor and the sphincter. PVR urine volume is measured by US. The main limitation of uroflowmetry is the compliance of the child to follow instructions [697-700].

3.13.3.5 Urodynamic studies

The standards of the ICCS should be applied to UDs in patients with neurogenic bladders and accordingly reported [571, 683]. Natural fill UD in children with neurogenic bladder detects more overactivity compared with diagnoses delivered by conventional UD [701, 702]. It may be an option in patients where the findings in the conventional UD are inconsistent with clinical symptoms and other clinical findings [702].

3.13.3.6 Voiding cystourethrogram

If video-urodynamic equipment is not available, a VCUG with UD is an alternative to confirm or exclude VUR and visualise the LUT including the urethra.

3.13.3.7 Renal scan

DMSA (Technetium Dimercapto-Succinic Acid) Renal scan is the gold standard to evaluate renal parenchyma. In contemporary series, renal scars can be detected in up to 46% as patients get older [703-705]. In a recent study 4 out of 68 children had renal scarring, 3 had a history of febrile UTI and one a vesicoureteral reflux [655]. A positive DMSA-Scan correlates well with hypertension in adulthood, whereas US has a poor correlation with renal scars [705]. Therefore, a DMSA scan as a baseline evaluation in the first year of life is recommended.

3.13.4 ***Management***

The medical care of children with neurogenic bladder requires an on-going multidisciplinary approach. There is some controversy about optimal timing of the management; proactive vs. expectant management [706-708]. Even with a close expectant management e.g. in one series 11 out of 60 need augmentation within a follow-up of 16 years and 7 out of 58 had a decrease in total renal function, which was severe in two [709]. During the treatment it should also be taken into account in spina bifida patients, that QoL is related to urinary incontinence independent of the type and level of spinal dysraphism and the presence or absence of a liquor shunt [710].

Foetal open and endoscopic surgery for meningomyelocele are performed to close the defect as early as possible in order to reduce neurological, orthopaedic and urological problems [711]. In the MOMS-Trial, Brooks *et al.* found no difference between those closed in utero vs. those closed after birth concerning the need for CIC [677], but less bladder trabeculation was found in the prenatal surgery group. Mean gestation age (28.3 vs. 35.2) seems to have no initial impact on bladder function in the first few years of life [712]. Two European series showed, that there is a possible benefit of open intrauterine closure on urinary continence showing normal bladder function in up to 33% at least in the first 2-3 years of life [713] [714]. Despite these promising reports [712, 715-717], caregivers need to be aware of the high risk of developing a neurogenic bladder as demonstrated by a Brazilian group [718]. Regular and close follow-up examinations including UD are indicated in all these patients.

3.13.4.1 Early management with intermittent catheterisation

Starting intermittent catheterisation (IC) soon after birth and closure of the defect by the neurosurgeon in all infants has shown to decrease renal complications and the need for later augmentation [719-722]. In infants without any clear sign of outlet obstruction, this may be delayed but only in very selected cases. These infants should be monitored very closely for UTIs and changes of the urinary tract with US and UD. The early initiation of CIC in the new-born period makes it easier for caregivers to master the procedure and for children to accept it, as they grow older [723, 724]. Up to 90% of patients will perform CIC [725].

A Cochrane review as well as a recent study showed, that there is a lack of evidence to state that the incidence of UTI is affected by use of sterile or clean technique, coated or uncoated catheters, single (sterile) or multiple use (clean) catheters, self-catheterisation or catheterisation by others, or by any other strategy [726-730]. Looking at the microbiological milieu of the catheter, there was a trend for reduced recovery of potentially pathogenic bacteria with the use of hydrophilic catheters. Also, a trend for a higher patient satisfaction with the use of hydrophilic catheters was seen [731]. Based on the current data, it is not possible to state that one catheter type, technique or strategy is better than any other.

3.13.4.2 Medical therapy

Antimuscarinic/anticholinergic medication reduces/prevents detrusor overactivity and lowers intravesical pressure [732, 733]. Effects and side effects depend on the distribution of the M1-M5 receptors [734]. In the bladder, the subtype M2 and M3 are present [733, 735]. Oxybutynin is the most frequently used in children with neurogenic bladder with a success rate of up to 93% [736, 737]. Dose-dependent side-effects (such as dry mouth, facial flushing, blurred vision heat intolerance etc.) limit its use. Intravesical administration gives a significant higher bioavailability due to the circumvention of the intestinal first pass metabolism, as well as possible local influence on C-fiber-related activity and can be responsible for different clinical effect [738, 739].

Intravesical administration should be considered in patients with severe side-effects, as long-term results demonstrated that it was well-tolerated and effective [740, 741]. Transdermal administration also leads to a substantially lower ratio of N-desethyloxybutynin to oxybutynin plasma levels, however, there are treatment-related skin reactions in 12 out of 41 patients [742]. There are some concerns about central anticholinergic adverse effects associated with oxybutynin [743, 744]. A double blinded cross-over trial, as well as a case control study, showed no deleterious effect on children's attention and memory [705, 745] . Tolterodine, solifenacine, fesoterodin, trospium chloride and propiverine and their combinations can also be used in children [746-754].

The oral dosage for oxybutynin is up to 0.2 mg/kg [733] given three times daily. The intravesical dosage can be up to 0.7 mg/kg/daily and transdermal 1.3-3.9 mg/daily. The dosage of the other drugs is: Tolterodine 0.5 – 4 mg/day divided in two doses, Solifenacin 1.25 up to 10 mg per day (single dose), fesoterodine 4-8 mg per day (single dose) Propiverin 0.8 mg/kg/day divided in two dosages and trospium chloride up to 3 times 15 mg starting with 3 times 5 mg. Except for oxybutynin, all other anticholinergic drugs are off-label use, which should be explained to the caregivers.

Early prophylactic treatment with anticholinergics showed a lower rate of renal deterioration as well as a lower rate of progression to bladder augmentation [719, 755]. Beta-3 agonists like mirabegron as an adjuvant treatment has been shown to be effective and safe in some recent studies of children (> five years) and adolescents [756-759].

Alpha-adrenergic antagonists may facilitate emptying in children with neurogenic bladder [760]. Doxazosin with an initial dose of 0.5 to 1.0 mg or tamsulosin hydrochloride in a medium (0.0002-0.0004 mg/kg/day) or high dose (0.0004-0,0008 mg/kg/day) has been given to children with neurogenic bladders [760-762]. It was well tolerated but not effective at least in one study [761].

Botulinum toxin A injections: In neurogenic bladders that are refractory to anticholinergics, the off-label use of suburothelial or intramuscular injection of onabotulinum toxin A into the detrusor muscle is a treatment option [653, 654]. In children, continence could be achieved in 32-100% of patients, a decrease in maximum detrusor pressure of 32% to 54%, an increase of maximum cystometric capacity from 27% to 162%, and an improvement in bladder compliance of 28%-176% [653]. Onabotulinum toxin A seems to be more effective in bladders with obvious detrusor muscle over-activity, whereas non-compliant bladders without obvious contractions are unlikely to respond [763, 764]. Also, the injections into the trigone seems to be save in regard of reflux and upper tract damage; if it has some benefit is not further investigated [657]. Of the patients with failed augmentation cystoplasty, 43% responded well to intra-detrusor onabotulinum toxin A injections in a recent series of 30 patients [765].

The most used dose of onabotulinum toxin A is 10 to 12 U/kg with a maximum dose between 200 U and 360 U [766]. A randomized trail demonstrated, that 200IE have greater efficacy in reducing bladder pressure and increasing bladder capacity compared to 50 or 100IE [767]. Onabotolinum toxin A can be effective between three to twelve (0-25) months and repeated injections are effective up to ten years in one study [768-770].

Urethral sphincter onabotulinum toxin A 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 [771, 772].

Neuromodulation
Intravesical electrical stimulation of the bladder [773-775], sacral nerve stimulation [776, 777] and transcutaneous neuromodulation [668] are still experimental and cannot be recommended outside of clinical trials. The same is true for the intradural somatic-to-autonomic nerve anastomosis[778, 779].

Urethral Dilatation
The aim is to lower the pop-off pressure by lowering the detrusor leak-point pressure by dilatation of the external sphincter under general anaesthesia up to 36 Charr. Some studies showed, that especially in females, the procedure is safe and in selected patients, effective [780-782].

Vesicostomy
Vesicostomy - preferably a Blocksom stoma [783] - is an option to reduce bladder pressure in children/ new-borns, if the caregivers are incompliant with IC and/or IC through the urethra is extremely difficult or impossible [784]. Especially in the young infant with severe upper tract dilatation or infections, a vesicostomy should be considered. In some patients it may be also a good long-term solution to prevent infection and renal deterioration [785]. Drawbacks are the difficulty fitting and maintaining a collecting appliance in older patients. A cystostomy button may be an alternative, with a complication rate (mostly UTI) of up to 34% within a mean follow-up of 37 months [786].

3.13.4.3 Management of faecal incontinence
Children with neurogenic bladder usually have also a neurogenic bowel function. Faecal incontinence may have an even greater impact on QoL, as the odour can be a reason for social isolation. The aim of each treatment is to obtain a smooth, regular bowel emptying and to achieve continence and impendence. The regime should be tailored to the patient's need, which may change over time. Beside a diet with small portioned fibre food and adequate fluid intake to keep a good fluid balance [733], follow-up options should be offered to the patients and caregivers.

In the beginning, faecal incontinence is managed most commonly with mild laxatives, such as mineral oil, combined with enemas to facilitate removal of bowel contents. To enable the child to defecate once a day at a given time, rectal suppositories as well as digital stimulation by parents or caregivers can be used. Today, transanal irrigation is one of the most important treatments for patients with neurogenic bowel incontinence. Regular irrigations significantly reduce the risk for faecal incontinence also in the long run in up to 90% of the patients [787]. The risk of irrigation induced perforation of the bowel is estimated as one per 50,000 [678]. During childhood, most children depend on the help of the caregivers. Later in some patients, transanal irrigation becomes difficult or impossible due to anatomic or social circumstances. In these patients antegrade irrigation using a MACE-stoma (Malone Antegrade Continence Enema) is an option, which can also be placed in the left abdomen [788, 789]. In a long-term study of 105 patients with a MACE stoma, 69% had successful bowel management. They were started on normal saline, but some switched to GoLYTELY (PEG-3350 and electrolyte solution). Additives (biscodyl, glycerin etc.) were needed in 34% of patients. Stomal complications occurred in 63% (infection, leakage, and stenosis) of patients, 33% required surgical revision and 6% eventually required diverting ostomies [790]. In addition, patients need to be informed, that the antegrade irrigation is also time consuming taking at least 20-60 minutes.

3.13.4.4 Urinary tract infection
Urinary tract infections are common in children with neurogenic bladders. However, there is no consensus in most European centres, for prevention, diagnosing and treating UTIs in children with neurogenic bladders performing CIC [791]. Although bacteriuria is seen in more than half of children on CIC, patients who are asymptomatic do not need treatment [792]. Continuous antibiotic prophylaxis (CAP) creates more bacterial resistance as demonstrated by a randomized study. Those that stopped the prophylaxis had reduced bacterial resistance, however, 38 out of 88 started antibiotic prophylaxis again due to recurrent UTIs or the caregivers request [793]. A cohort study with 20 patients confirmed these findings. Continuous antibiotic prophylaxis was not protective against the development of symptomatic UTIs and new renal scarring but increased the risk of bacterial resistance [794]. A randomized study in 20 children showed that cranberry capsules significantly reduced the UTI-rate as well as the rate of bacteriuria [795]. If VUR is present, prophylactic antibiotics should be started when patients experience recurrent UTIs [796, 797].

3.13.4.4.1 Urinary tract infection and clean intermittent catheterisation

The incidence of asymptomatic bacteriuria ranges between 42%-76% [723, 733, 798]. A cross-over study in 40 children with neurogenic bladder demonstrated, that the reuse of CIC-catheters for up to three weeks compared to one week increased the prevalence of bacteriuria from 34% to 74% (it was 60% at the start of the study). During the study-period of eighteen weeks, none of the patients developed a febrile UTI [799]. There is no medical benefit in performing CAP in children with neurogenic bladder, who perform CIC [733]. In those with recurrent UTI, intravesical instillation of gentamycin or neomycin/polymyxin may be an option [800, 801].

Reflux

Secondary reflux in patients with neurogenic bladder increases the risk for pyelonephritis. The treatment is primary related to bladder function including anticholinergic therapy, CIC and may be later augmentation [802]. Those with early and post-therapy persistent reflux during videourodynamic studies at low pressure have a higher risk of pyelonephritis [803]. Patients with a high-grade reflux before augmentation have a higher risk of persistent symptomatic reflux after the enterocystoplasty [804]. Therefore simultaneous ureteral re-implantation in high-grade symptomatic reflux especially in those with low-pressure high-grade reflux should be discussed with the patient/caregivers. Endoscopic treatment has a failure rate of up to 75% after a median follow-up of 4.5 years [805] which is in contrast to the open techniques with a higher success rate but may have an increased risk of inducing obstruction [806].

3.13.4.5 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 [807]. The prevalence of precocious puberty is higher in girls with meningomyelocele [808]. 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.

Women seem to be more sexually active than men in some studies from the Netherlands and the USA [807, 809]. The level of the lesion was the main predictor to be sexually active [810, 811]. Erectile function can be improved by sildenafil in up to 80% of the male patients [812, 813] . Neurosurgical anastomosis between the inguinal nerve and the dorsal penile nerve in patients with a lesion below L3 and disturbed sensation is still to be considered as an experimental treatment [809, 814]. Only 17% to one third of the patients talk to their doctors about sexuality, 25–68% were informed by their doctors about reproductive function [807]. Continence seems to play an important role too. Nine out eleven females without sexual dysfunction reported continence, whereas 50 out of 59 with sexual dysfunction have some urinary incontinence in a recent study [815]. Therefore, early discussion about sexuality in the adolescent is recommended and should be promoted by the paediatric urologist taking care of these patients.

3.13.4.6 Bladder augmentation

In patients where conservative treatment including onabotulinum toxin A (for indication see 3.12.4.3) fails to keep a low-pressure reservoir with a good capacity and compliance, bladder augmentation should be offered. For augmentation, ileal and colonic segments can be used [816]. Gastric segments are rarely used due to its associated complications like the haematuria-dysuria syndrome as well as secondary malignancies, which arise earlier than with other intestinal segments [817-820]. Enterocystoplasty increases bladder capacity, reduces storage pressure and can improve UUT drainage [821]. A good socially acceptable continence rate can be achieved with or without additional bladder outlet procedures [822]. In those, who are not able to perform CIC through the urethra, a continent cutaneous channel should be offered. One recent study in 10 patients showed that thoracic epidural analgesia appears to be a safe and effective opioid sparing option to assist with postoperative pain management following lower urinary tract reconstruction [823]. Surgical complications and revision rate in this group of patients is high. The 30-day all over event rate in the American College of Surgeons' National Surgical Quality Database is approximately 30% (23-33%) with a re-operation rate in this short time period of 13% [824, 825]. In these patients with long-life expectancy the complication rate clearly increases with the follow-up period [826]. The ten-year cumulative complication incidence from the Paediatric Health Information System showed a rate of bladder rupture in up to 6.4%, small bowel obstruction in up to 10.3%, bladder stones in 36%, pyelonephritis in more than a third of the patients and a re-augmentation rate of up to 13% [827]. Bladder perforation, as one of the worst complications, occurs in 3-13% [828]. The rate of VP-shunt infections after gastrointestinal and urological procedures ranges between 0-22%. In a recent study, bowel preparation seems not to have a significant influence on the infection rate (10.5% vs. 8.3%) [829]. Not only surgical complications must be considered; also metabolic complications and consequences after incorporating bowel segments have to be taken into account, such as imbalance of the acid base balance, decrease in vitamin

B12 levels and loss of bone density. Stool frequency can increase as well as diarrhoea after exclusion of bowel segments [830] and last, but not least, these patients have a lifelong increased risk to develop secondary malignancies [831, 832]. Therefore, a lifelong follow-up of these patients is required including physical examination, US, blood gas analysis, (pH and base excess), renal function and vitamin B12 if Ileum is used. Endoscopic evaluation starting ten years after augmentation is not cost-effective [833, 834], but may prevent some advanced cancer. Woodhouse *et al.* do not recommend cystoscopy within the first fifteen years after surgery [835]. The real value of annual cystoscopic evaluation has not been proven by any study. Urodynamic studies after bladder augmentation are only indicated, if upper tract dilatation and/or incontinence after the operation has not improved [836].

Adverse effects of intestinal cystoplasties can be avoided by the use of ureterocystoplasty. The combination of a small contracted bladder, associated with a severe dilation of the ureter of a non-functioning kidney is quite rare. The technique was first described in 1973 by Eckstein [837]; the success rate depends on patient selection and the re-augmentation rate can reach 73% [838, 839].

Auto-augmentation with partial detrusorectomy or detrusormyotomy creating a diverticulum avoids metabolic complications with the use of intestinal segments. The reports are conflicting, therefore, it may be used in selected cases [840-843]. For a successful outcome, a pre-operative bladder capacity of 75-80% of the expected volume seems necessary [841, 844]. Seromuscular cystoplasty has also not proven to be as successful as standard augmentation with intestine [845]. Tissue engineering, even if successful in vitro and some animal models, does not reach the results by using intestinal segments with a higher complication rate [846, 847]. Therefore, these alternatives for bladder augmentation should be considered as experimental and should be used only in controlled trials.

3.13.4.7 Bladder outlet procedures

No available medical treatment has been validated to increase bladder outlet resistance. Alpha-adrenergic receptor stimulation of the bladder neck has not been effective [760]. Using fascial slings with autologous fascial strip or artificial material a continence rate between 40-100% can be achieved. In most cases this is achieved in combination with bladder augmentation [848-853]. Catheterising through a reconstructed bladder neck or a urethra compressed by a sling may not be easy; many surgeons prefer to combine this approach with a catheterisable channel [706]. In contrast to the autologous slings, artificial slings in girls with CIC through the urethra have a high complication rate [854]. In males, it may be an option [855], however as long as long-term results are missing, this method has to be classified as experimental and should only be carried out in studies. Artificial urinary sphincters were introduced by Scott in 1973 [856]. The continence rates in the literature in selected patients can be up to 83% [857, 858]. Post-pubertal patients, who can void voluntary are good candidates, if they are manually dexterous. In very selected patients, CIC through the sphincter in an augmented bladder is possible [858]. The erosion rate can be up to 29% and the revision rate up to 100% depending on the follow-up time [852].

Patients, who underwent a bladder neck procedure only, have a chance of > 30% for an augmentation and/or onabotulinum toxin A injections >30% later on; half of them developed new upper tract damage in that time [859-861]. In patients with a good bladder capacity and bladder compliance without an indication for bladder augmentation, up to 40% will need augmentation later on [860]. Therefore, close follow-up of these patients with UD is required to avoid upper tract damage and chronic renal failure.

Bladder neck reconstruction is used mostly in exstrophy patients with acceptable results. However, in children with a neurogenic bladder the results are less favourable [862]. In most patients, the creation of a continent catheterisable stoma is necessary due to difficulties in performing the CIC via the urethra. In one series, 10% to a third still performed CIC via the urethra with a re-operation rates between 67% and 79% after a median follow-up between seven and ten years [863]. In patients who are still incontinent after a bladder outlet procedure, bladder neck closure with a continent catheterisable stoma is an option. The combination of a sling procedure together with a urethral lengthening procedure may improve the continence rates [864].

Bulking agents have a low success rate (10-40%), which is in most cases only temporary [865-867]. However, it does not adversely affect the outcome of further definite surgical procedures [865].

Bladder neck closure is often seen as the last resort to gain urinary continence in those patients with persistent urinary incontinence through the urethra. In girls, the transection is done between bladder neck and urethra and in boys above the prostate with preservation of the neurovascular bundle. It is an effective method to achieve continence together with a catheterisable cutaneous channel +/- augmentation as a primary or secondary

procedure [868, 869]. A complication rate of up to a third and a vesicourethral/vesicovaginal fistula in up to 15% should be considered [870], together with a higher risk for bladder stones, bladder perforation and deterioration of the upper tract function, if the patient is not compliant with CIC and bladder irrigations [870, 871].

3.13.4.8 Catheterisable cutaneous channel

In most patients with a neurogenic bladder CIC is required. If this is not possible, or very time and/or resource consuming via the urethra, a continent cutaneous catheterisable channel should be offered as well as in those with bladder outlet procedures. It is especially beneficial to wheelchair-bound patients who often have difficulty with urethral catheterisation or are dependent on others to catheterise the bladder. In long-term studies the revision rate due to stenosis or incontinence can be as high as 50-60% depending on the type of channel [872, 873].

The stoma can be placed at the umbilicus or in the lower right abdominal wall using a VQZ plasty [874]. It should be carefully evaluated pre-operatively: it is extremely important that the patient can reach the stoma easily. Sometimes it has to be placed in the upper abdominal wall due to sever scoliosis mostly associated with obesity.

3.13.4.9 Continent and incontinent cutaneous urinary diversion

Incontinent urinary diversion should be considered in patients who are not willing or able to perform a CIC and who need urinary diversion because of upper tract deterioration or gain urinary continence due to social reasons. In children and adolescents, the colonic conduit has shown to have less complications compared to the ileal conduit [875-878]. Total bladder replacement is extremely rare in children and adolescents, but may be necessary in some adults due to secondary malignancies or complications with urinary diversions. 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 [822, 879, 880].

Algorithms can be used for management of these patients (Figures 8 and 9).

3.13.5 ***Follow-up***

Neurogenic bladder patients require lifelong follow-up including not only urological aspects but also neurological and orthopaedic aspects. Regular investigation of upper and lower urinary tract is mandatory. In patients with changes of the function of the upper and/or lower urinary tract, a complete neurological re-investigation should be recommended including a total spine MRI to exclude a secondary tethered cord or worsening of the hydrocephalus. In addition, if some neurological changes are observed a complete investigation of the urinary tract should be undertaken.

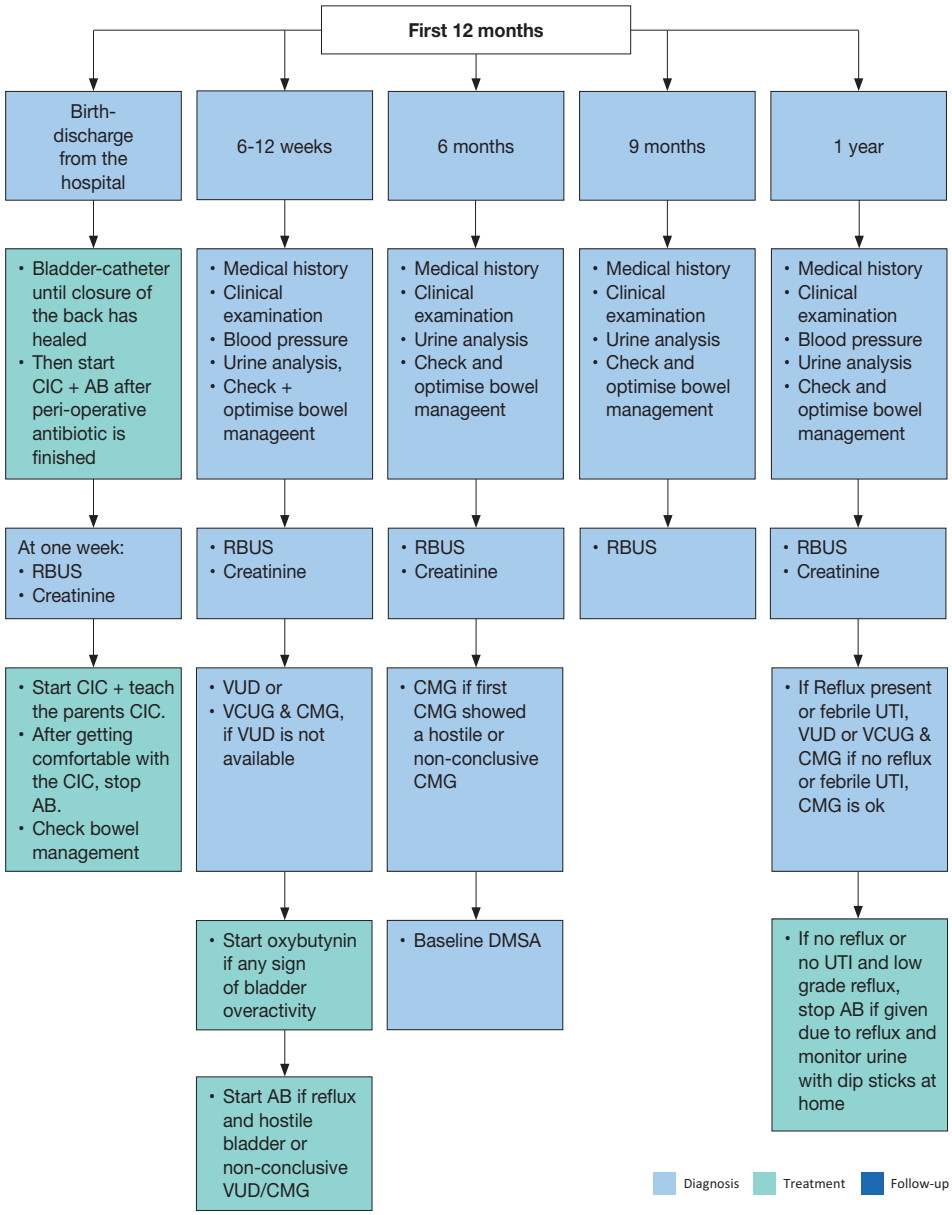
A recent study of this guideline panel revealed that the priorities of patients for future expectations were as following in decreasing order: GoL, surgical techniques, development of new medications and sexuality/fertility issues. Male spina bifida patients preferred new medications and sex/fertility issues more, whereas females favoured QoL issues improvement more. These factors should be considered during long-term management [2].

In those patients with urinary tract reconstruction using bowel segments, regular investigations concerning renal function, acid base balance and vitamin B12 status are mandatory to avoid metabolic complications. There is an increased risk for secondary malignancies in patients with a neurogenic bladder either with or without enteric bladder augmentations [881-885]. Therefore, patients need to be informed of this risk and possible signs like haematuria. Although there are insufficient data on follow-up schemes to discover secondary malignancies, after a reasonable follow-up time (e.g. ten to fifteen years), an annual cystoscopy can be considered.

3.13.6 ***Self-organisation of patients***

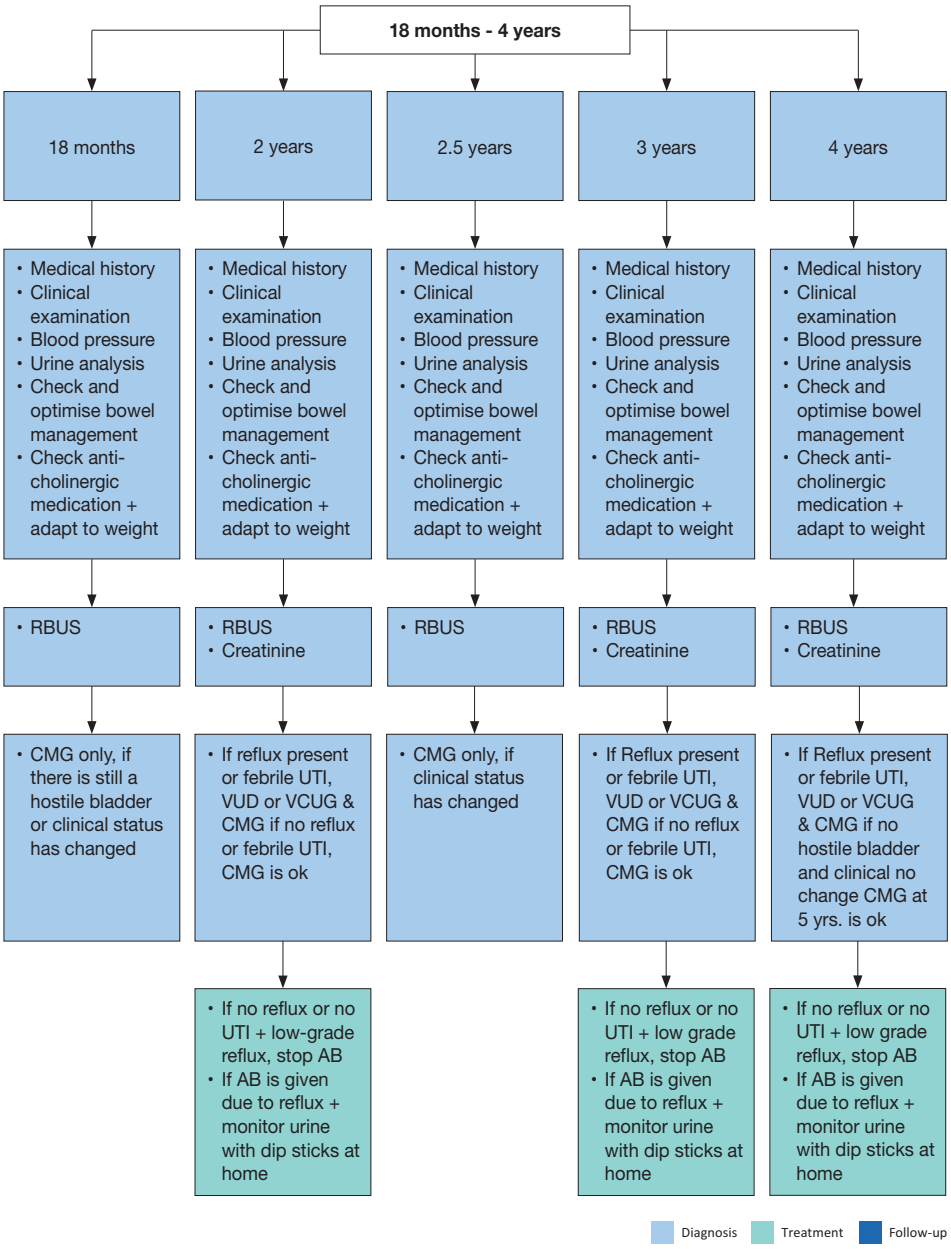
As patients' self-organisations can support the parents, caregivers and the patients in all aspects of their daily life, patients should be encouraged to join these organisations.

Figure 8a: Management of children with myelodysplasia with a neurogenic bladder Flowchart - First year of life



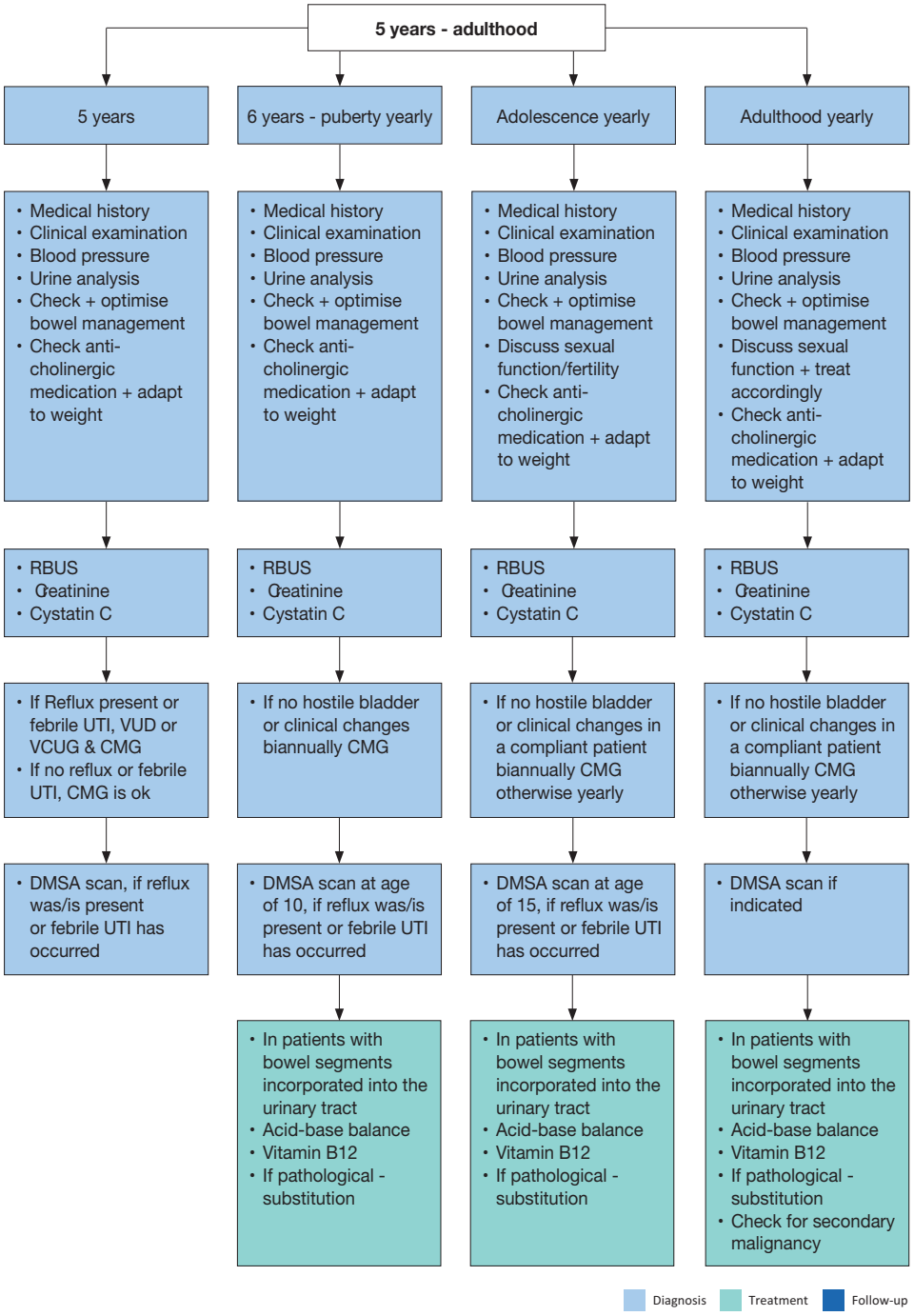
RBUS = Renal bladder ultrasound; UTI = urinary tract infection; VUD = videourodynamic; VCUG = voiding cystourethrography; CMG = cystometrogram; DMSA = dimercaptosuccinic acid; AB = antibiotics.

Figure 8b: Management of children with myelodysplasia with a neurogenic bladder Flowchart - 18 months - 4 years of age



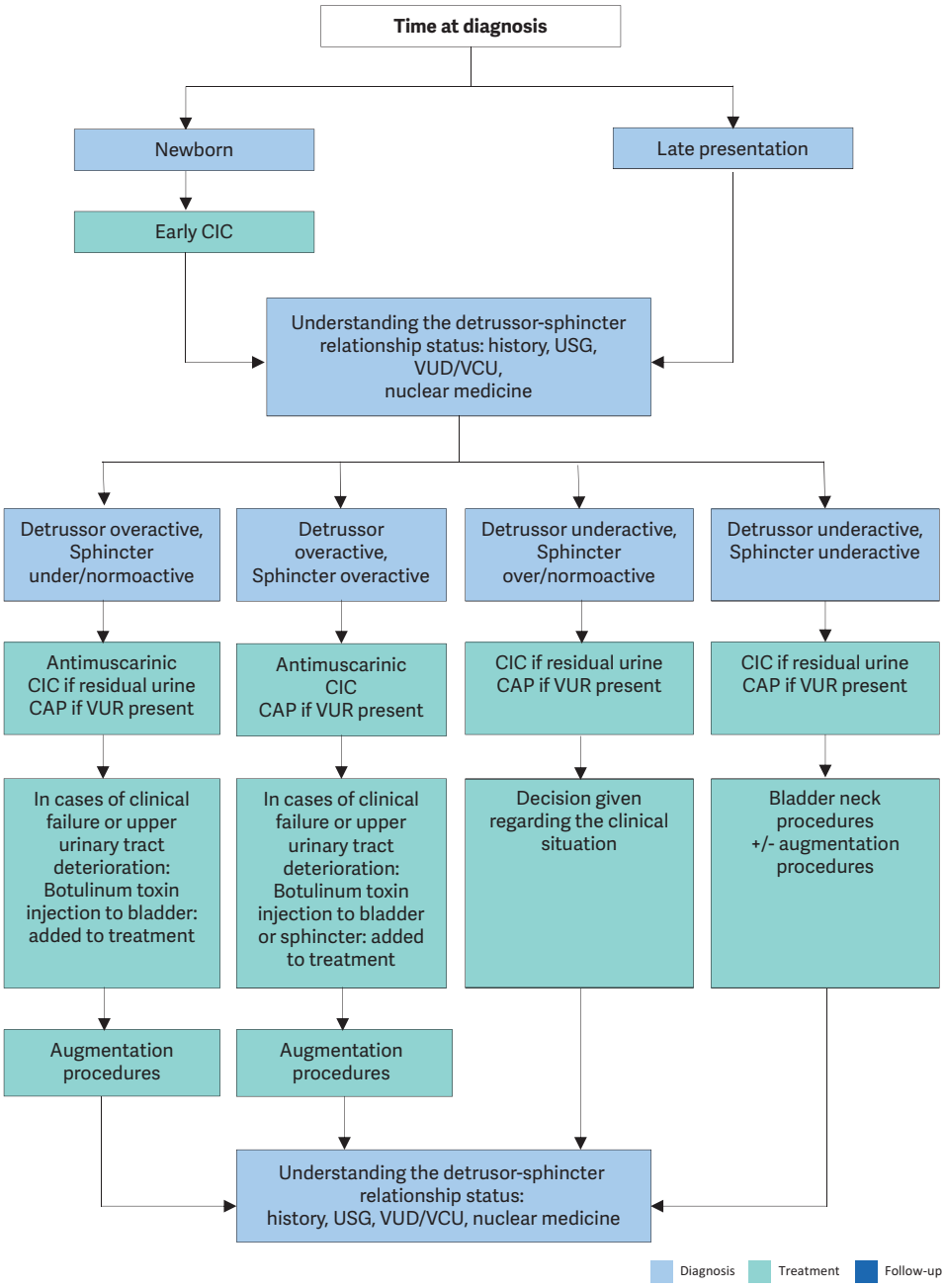
RBUS = Renal bladder ultrasound; UTI = urinary tract infection; VUD = videourodynamic; VCUG = voiding cystourethrography; CMG = cystometrogram; DMSA = dimercaptosuccinic acid; AB = antibiotics

Figure 8c: Management of children with myelodysplasia with a neurogenic bladder Flowchart - 5 years to adulthood



RBUS = Renal bladder ultrasound; UTI = urinary tract infection; VUD = videourodynamic; VCUG = voiding cystourethrography; CMG = cystometrogram; DMSA = dimercaptosuccinic acid.

Figure 9: Algorithm for the management of children with myelodysplasia with a neurogenic bladder



CAP = continuous antibiotic prophylaxis; CIC = clean intermittent catheterisation; US = ultrasound; VCUG = voiding cystourethrography; VUD = videourodynamic; VUR = vesicoureteric reflux.

3.13.7 Summary of evidence and recommendations for the management of neurogenic bladder

Summary of evidence	LE
Neurogenic detrusor-sphincter dysfunction (NDSD) 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	Strength rating
Urodynamic studies should be performed in every patient with spina bifida as well as in every child with high suspicion of a neurogenic bladder to estimate the risk for the upper urinary tract and to evaluate the function of the detrusor and the sphincter.	2	Strong
In all newborns, intermittent catheterisation (IC) should be started soon after birth. In those with a clear underactive sphincter and no overactivity, starting IC may be delayed. If IC is delayed, closely monitor babies for urinary tract infections, upper tract changes (US) and the lower tract (UD).	3	Strong
Start early anticholinergic medication in the newborns with suspicion of an overactive detrusor.	2	Strong
The use of suburothelial or intradetrusoral injection of onabotulinum toxin A is an alternative and a less invasive option in children who are refractory to anticholinergics in contrast to bladder augmentation.	2	Strong
Treatment of faecal incontinence is important to gain continence and independence. Treatment should be started with mild laxatives, rectal suppositories as well as digital stimulation. If not sufficient transanal irrigation is recommended, if not practicable or feasible, a Malone antegrade colonic enema (MACE)/Antegrade continence enema (ACE) stoma should be discussed.	3	Strong
Ileal or colonic bladder augmentation is recommended in patients with therapy resistant overactivity of the detrusor, small capacity and poor compliance, which may cause upper tract damage and incontinence. The risk of surgical and non-surgical complications and consequences outweigh the risk of permanent damage of the upper urinary tract +/- incontinence due to the detrusor.	2	Strong
In patients with a neurogenic bladder and a weak sphincter, a bladder outlet procedure should be offered. It should be done in most patients together with a bladder augmentation.	3	Weak
Creation of a continent cutaneous catheterisable channel should be offered to patients who have difficulties in performing an IC through the urethra.	3	Weak
A life-long follow-up of renal and reservoir function should be available and offered to every patient. Addressing sexuality and fertility starting before/during puberty should be offered.	3	Weak
Urinary tract infections are common in children with neurogenic bladders, however, only symptomatic UTIs should be treated.	3	Weak

3.14 Dilatation of the upper urinary tract (UPJ and UVJ obstruction)

3.14.1 Epidemiology, aetiology and pathophysiology

Dilatation of the upper urinary tract (UUT) remains a significant clinical challenge in deciding which patient will benefit from treatment. Ureteropelvic junction (UPJ) obstruction is defined as impaired urine flow from the pelvis into the proximal ureter with subsequent dilatation of the collecting system and the potential to damage the kidney. It is the most common pathological cause of neonatal hydronephrosis [886]. 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 pathological neonatal hydronephrosis. They occur more often in males and are more likely to occur on the left side [887]. 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 [888].

*3.14.2 **Diagnostic evaluation***

The widespread use of US during pregnancy has resulted in a higher detection rate for antenatal hydronephrosis [889]. The challenge in the management of dilated UUT is to decide which child should be observed, which should be managed medically, and which 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 10).

3.14.2.1 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 [890].

3.14.2.2 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 [891]. 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.

3.14.2.3 Voiding cystourethrogram

In newborns with identified UUT dilatation, the primary or important associated factors that must be detected include:

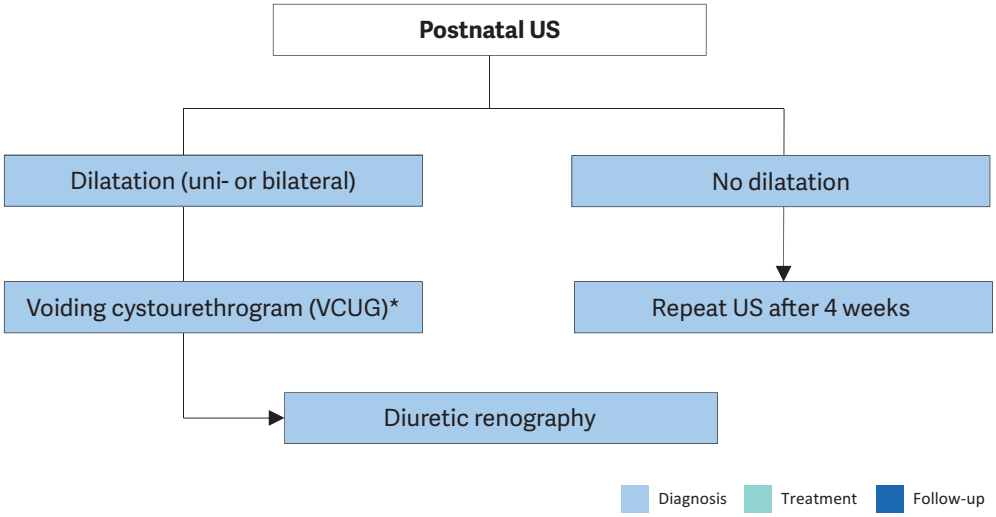
- vesicoureteral reflux (found in up to 25% of affected children) [892];
- urethral valves;
- ureteroceles;
- diverticula;
- neurogenic bladder.

Conventional VCUG is the method of choice for primary diagnostic procedures [893].

3.14.2.4 Diuretic renography

Diuretic renography is the most commonly used diagnostic tool to detect the severity and functional significance of problems with urine transport. Technetium-99m (99mTc) mercaptoacetyltriglycine (MAG3) is the radionuclide of choice. It is important to perform the study under standardised circumstances (hydration, transurethral catheter) after the fourth and sixth weeks of life [894]. Oral fluid intake is encouraged prior to the examination. At fifteen minutes before the injection of the radionuclide, it is mandatory to administer normal saline intravenous infusion at a rate of 15 mL/kg over 30 minutes, with a subsequent maintenance rate of 4 mL/kg/h throughout the entire time of the investigation [895]. The recommended dose of furosemide is 1 mg/kg for infants during the first year of life, while 0.5 mg/kg should be given to children aged one to sixteen years, up to a maximum dose of 40 mg.

Figure 10: Diagnostic algorithm for dilatation of the upper urinary tract



** A diagnostic work-up including VCUG must be discussed with the caregivers, 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 [803].*
US = ultrasound.

*3.14.3 **Management***

3.14.3.1 Prenatal management

Counselling the caregivers 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 caregivers 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 [896].

3.14.3.1.1 Antibiotic prophylaxis for antenatal hydronephrosis

The benefits and harms of continous antibiotic prophylaxis (CAP) vs. observation in patients with antenatal hydronephrosis are controversial. Currently, only two RCTs have been published, one of which is a pilot trial [897] and the other publication is only available as a congress abstract [898]. Both publications present incomplete data and outcomes.

The Panel conducted a SR assessing the literature from 1980 onwards [899]. The key findings are summarised below.

Due to the heterogeneity of the published literature it was not possible to draw strong conclusions as to whether CAP is superior to observation alone in children diagnosed with antibiotic prophylaxis for antenatal hydronephrosis (ANH). In the first RCT, a prospective longitudinal study [897], female gender, uncircumcised males, lack of CAP, high-grade hydronephrosis, hydroureteronephrosis and VUR were found to be the independent predictors for the development of UTI. The second RCT included in the SR, was published as an abstract only, presented limited data [898]. This trial seemed to focus mainly on patients with ANH and VUR and did not report any beneficial effect of CAP on UTI rates, but details on the study population were limited.

Key findings of the SR are that CAP may or may not be superior to observation in children with antenatal hydronephrosis in terms of decreasing UTI. Due to the low data quality it was also not possible to establish whether boys or girls are at a greater risk of developing a UTI, or ascertain whether the presence or absence of VUR impacts UTI rates. A correlation between VUR-grade and UTI could not be established either. However, noncircumcised infants, children diagnosed with high-grade hydronephrosis and hydroureteronephrosis were shown to be at higher risk of developing a UTI.

The SR also tried to identify the most effective antibiotic regimen and present data on adverse effects but, due to heterogeneity, the available data could not be statistically compared. The most commonly used antibiotic in infants with antenatal hydronephrosis is trimethoprim, but only one study reported side effects [897].

In conclusion, based on the available evidence, the benefits and harms of CAP in children with antenatal hydronephrosis remain unproven. Uncircumcised infants and infants with hydroureteronephrosis and highgrade hydronephrosis are more likely to develop a UTI. Continuous antibiotic prophylaxis should be reserved for this sub-group of children who are proven to be at high risk.

3.14.3.2 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. According to a Cochrane review, non-surgical management of unilateral UPJ obstruction in infants less than two years old is also an option. However the high risk of bias of the included studies limits the evidence of this systematic review [900].

Symptomatic obstruction (recurrent flank pain, UTI) requires surgical correction using a pyeloplasty, according to the standardised open technique of Hynes and Anderson [901]. 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. A recent interventional study suggested that, in operated infants less than six months, inserting a stent (transanastomotic stent) decreases the complication rates compared to stentless approach [902]. However the results should be taken cautiously since there are successful reported stentless procedures in other age groups.

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 [691].

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 [903, 904]. 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 [905]. Laparoscopic pyeloplasty can also be performed for re-do cases with the same advantages of the primary cases [906]. Robotic-assisted laparoscopic pyeloplasty (RALP) has all the same advantages as LP plus better manoeuvrability, improved vision, ease in suturing and increased ergonomics but higher costs [907, 908]. A recent study comparing RALP and LP has shown similar postoperative outcomes with exception of decreased operative time for RALP [909]. 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.

3.14.3.3 Megaureter

The treatment options of secondary megaureters are reviewed in Chapter 3.15.3.

3.14.3.3.1 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 [910]. 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 [911].

3.14.3.3.2 Surgical management

In general, surgery is indicated for symptomatic children, if there is a drop in function in conservative follow-up and hydroureteronephrosis is increasing [912]. Data suggest that children with a ureteric diameter of > 10-15 mm are more likely to require intervention [913].

The initial approach to the ureter can be either intravesical, extravesical or combined. Straightening the ureter is necessary without devascularisation. Ureteral tapering should enhance urinary flow into the bladder. The ureter must be tapered to achieve a diameter for an anti-reflux repair. Several tailoring techniques exist, such as ureteral imbrication or excisional tapering [914]. Some institutions perform endoscopic stenting, but there are still no long-term data and no prospective randomised trials to confirm their outcome. A systematic review assessed the success rates of endoscopic management of primary obstructive megaureters [915]. It was reported that endoscopic managements including; stent placement, balloon dilatation and incision can be an alternative

treatment in patients > 1 years of age. One third of those patients required further surgical correction. Furthermore, the long-term outcome of endoscopic management is still unknown. Therefore the EAU Paediatric Urology Guidelines Panel can not recommend endoscopic management routinely since the type of intervention and the management outcomes are unclear.

*3.14.4 **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 standardised and have a good clinical outcome.

*3.14.5 **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 pathological cause of hydronephrotic kidneys (40%).	1
In children diagnosed with antenatal hydronephrosis, a systematic review could not establish any benefits or harms related to continuous antibiotic prophylaxis.	1b
In children diagnosed with antenatal hydronephrosis, non-circumcised infants (LE: 1a), children diagnosed with high-grade hydronephrosis (LE: 2) and hydroureteronephrosis (LE: 1b) were shown to be at higher risk of developing UTI.	2

Recommendations	LE	Strength rating
Include serial ultrasound (US) and subsequent diuretic renogram and sometimes voiding cystourehrography in postnatal investigations.	2	Strong
Offer continuous antibiotic prophylaxis to the subgroup of children with antenatal hydronephrosis who are at high risk of developing urinary tract infection like uncircumcised infants, children diagnosed with hydroureteronephrosis and high-grade hydronephrosis, respectively.	2	Weak
Decide on surgical intervention based on the time course of the hydronephrosis and the impairment of renal function.	2	Weak
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	Weak
Offer pyeloplasty when ureteropelvic junction obstruction has been confirmed clinically or with serial imaging studies proving a substantially impaired or decrease in function.	2	Weak
Do not offer surgery as a standard for primary megaureters since the spontaneous remission rates are as high as 85%.	2	Strong

3.15 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 thus 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.

These Guidelines aim to provide a practical approach to the treatment of VUR based on risk analysis and selective indications for both diagnostics and intervention. Although the Panel have tried to summarise most of the possible scenarios in one single table, the table itself is still quite busy. The Panel strongly share the view that making simple and practical guidelines would underestimate the complexity of VUR as a sign of a wide range of pathologies [916]. In a recent publication the EAU and ESPU Pediatric Guidelines Panel summarized and updated this chapter [1611].

3.15.1 ***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. 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 [917]. Vesicoureteric reflux is a very common urological anomaly in children, with an incidence of nearly 1%.

Genetic analysis studies revealed monogenic causes for VUR and significant differentiation of innate immunity and epithelial function genes in children with VUR/UTIs compared to controls [918-920]. 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% [921]. Among infants prenatally identified with hydronephrosis on US, who were screened for VUR, the prevalence was 16.2% (7-35%) [922]. 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%) [922].

However, reflux detected by sibling screening is associated with lower grades [827] and significantly earlier resolution [923]. 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 [924].

The incidence of VUR is much higher among children with UTIs (30-50%, depending on age). Urinary tract infections are more common in girls than boys due to anatomical differences. However, among all children with UTIs, boys are more likely to have VUR than girls (29% vs. 14%). Boys also tend to have higher grades of VUR diagnosed at younger ages, although their VUR is more likely to resolve itself [925-928].

There is a clear co-prevalence between LUTD and VUR [929]. Lower urinary tract dysfunction refers to the presence of LUTS, including urge, urge incontinence, weak stream, hesitancy, frequency and UTIs, which reflect the filling and/or emptying dysfunction and may be accompanied with bowel problems [929]. Some studies have described a prevalence of 40-60% for VUR in children with LUTD [930]. A published Swedish Reflux trial has demonstrated LUTD in 34% of patients, and subdivision into groups characteristic of children revealed that 9% had isolated overactive bladder and 24% had voiding phase dysfunction [931].

The spontaneous resolution of VUR is dependent on age at presentation, sex, grade, laterality, mode of clinical presentation, and anatomy [932]. Faster resolution of VUR is more likely with age less than one year at presentation, lower grade of reflux (grade 1-3), and asymptomatic presentation with prenatal hydronephrosis or sibling reflux. The overall resolution rate is high in congenital high-grade VUR during the first years of life. In several Scandinavian studies, the complete resolution rate for high-grade VUR has been reported at > 25%, which is higher than the resolution rate for VUR detected after infancy [931, 933, 934].

The presence of renal cortical abnormality, bladder dysfunction, and breakthrough febrile UTIs are negative predictive factors for reflux resolution [935-937].

Dilating VUR increases the risk of developing acute pyelonephritis and renal scarring. Untreated recurrent UTIs may have a negative impact on somatic growth and medical status of the child. Evidence of renal scarring is present in 10-40% of children with symptomatic VUR, resulting from either congenital dysplasia and/or acquired post-infectious damage, which may have a negative impact on somatic growth and general well-being [938-940].

Scar rates vary in different patient groups. Patients with higher grades of VUR present with higher rates of renal scars. In those with prenatal hydronephrosis, renal scarring occurs in 10% of patients [941-946], whereas in patients with LUTD, this may increase up to 30% [704, 940, 947]. 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 [948].

3.15.2 ***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. Ultrasound

and VCUG could be considered as complementary techniques [949]. 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 [950]. In 1985, the International Reflux Study Committee introduced a uniform system for the classification of VUR [951, 952] (Table 2). 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 [952].

Radionuclide studies for detection of reflux have lower radiation exposure than VCUG, but the anatomical details depicted are inferior [953]. Recent studies on alternative imaging modalities for detection on VUR have yielded good results with voiding US and magnetic resonance VCUG [954-957]. Contrast enhanced voiding urosonography (ceVUS) with intravesical instillation of different ultrasound contrast agents has been shown to be highly sensitive giving comparable results with conventional VCUG while avoiding exposure to ionising radiation [510, 958-960]. 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. Intrarenal reflux (IRR) is associated with renal scarring development and it can be diagnosed on the images acquired during the voiding phase of the standard 4-staged VCUG and on ceVUS [961, 962].

Table 2: Grading system for VUR on VCUG, according to the International Reflux Study Committee [963].

Grade I	Reflux does not reach the renal pelvis; varying degrees of ureteral dilatation
Grade II	Reflux reaches the renal pelvis; no dilatation of the collecting system; normal fornices
Grade III	Mild or moderate dilatation of the ureter, with or without kinking; moderate dilatation of the collecting system; normal or minimally deformed fornices
Grade IV	Moderate dilatation of the ureter with or without kinking; moderate dilatation of the collecting system; blunt fornices, but impressions of the papillae still visible
Grade V	Gross dilatation and kinking of the ureter, marked dilatation of the collecting system; papillary impressions no longer visible; intraparenchymal reflux

Dimercaptosuccinic acid is the best nuclear agent for visualising the cortical tissue and differential function between both kidneys. Dimercaptosuccinic acid is taken up by proximal renal tubular cells and is a good indicator of renal parenchyma function. In areas of acute inflammation or scarring, DMSA uptake is poor and appears as cold spots. Dimercaptosuccinic acid scans are therefore used to detect and monitor renal scarring. A baseline DMSA scan at the time of diagnosis can be used for comparison with successive scans later during follow-up [964]. Dimercaptosuccinic acid can also be used as a diagnostic tool during suspected episodes of acute pyelonephritis [965]. Children with a normal DMSA scan during acute UTI have a low-risk of renal damage [965, 966].

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 PUV. In the case of LUTS, diagnosis and follow-up can be limited to non-invasive tests (e.g. voiding charts, US, or uroflowmetry) [929]. Cystoscopy has a limited role in evaluating reflux, except for infravesical obstruction or ureteral anomalies that might influence therapy.

3.15.2.1 Recommendations for diagnosis of VUR

Recommendations	**Strength rating**
For diagnosis of VUR apart from VCUG , ceVUS is another option.	Weak

3.15.2.2 Infants presenting with 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 [967, 968].

Ultrasound should be delayed until the first week after birth because of early oliguria in the neonate. It is essential to evaluate the bladder, as well as the kidneys. The degree of dilatation in the collecting system under US, when the bladder is both full and empty, may provide significant information about the presence of VUR. Bladder wall thickness and configuration may be an indirect sign of LUTD and reflux. The absence of hydronephrosis on postnatal US excludes the presence of significant obstruction; however, it does not exclude VUR.

Monitoring with careful US avoids unnecessary invasive and irradiating examinations. The first two

US scans within the first one to two months of life are highly accurate for defining the presence or absence of renal pathology. In infants with two normal, successive scans, VUR is rare, and if present it is likely to be low-grade [941, 969]. 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 [922]. 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 [922]. Dimercaptosuccinic acid provides more reliable and quantitative measurement of the degree of cortical abnormalities, first detected with US.

The use of VCUG is recommended in patients with US findings of bilateral high-grade hydronephrosis, duplex kidneys with hydronephrosis, ureterocele, ureteric dilatation, and abnormal bladders, because the likelihood of VUR is much higher. In all other conditions, the use of VCUG to detect reflux is optional [922, 943, 970-972].

When infants who are diagnosed with prenatal hydronephrosis become symptomatic with UTIs, further evaluation with VCUG should be considered [971]. Patients with severe hydronephrosis and those whose hydronephrosis is sustained or progressive, need further evaluation to exclude obstruction.

3.15.2.3 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. In screened populations the prevalence of VUR is 27.4% in siblings and 35.7% in offspring [963]. 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%). Although early screening and therefore early diagnosis and treatment appears to be more effective than late screening in preventing further renal damage [922, 924, 973, 974], screening in all siblings and offspring cannot be recommended based on the available evidence. The lack of RCTs for screened patients to assess clinical health outcomes makes evidence-based guideline recommendations difficult.

3.15.2.4 Recommendations for paediatric screening of VUR

Recommendations	Strength rating
Inform parents of children with vesicoureteric reflux (VUR) that siblings and offspring have a high prevalence of VUR.	Strong

3.15.2.5 Children with febrile urinary tract infections

A routine recommendation of VCUG at zero to two years of age after the first proven febrile UTI is the safest approach as the evidence for the criteria to selecting patients for reflux detection is weak. Upon diagnosing a child with the first febrile UTI, the risk factors: age (> 6 months), presence of sepsis, WBC count (≥ 15 000/mm), and abnormal renal US results, can be used for the generation of a predictive score for VUR presence [975]. (See Section 3.9 on urinary tract infections in children).

Children with febrile infections and abnormal renal US findings may have higher risk of developing renal scars and they should all be evaluated for reflux [513]. 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 identify 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 [503, 976-978].

3.15.2.6 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 [928, 979]. The co-existence of both conditions should be explored in any patient who has VUR. If there are symptoms suggestive of LUTD (e.g. urgency, wetting, constipation or holding manoeuvres), an extensive history and examination, including voiding charts, uroflowmetry and residual urine determination, will reliably diagnose underlying LUTD.

Among toilet-trained children, those with both LUTD and VUR are at higher risk of developing recurrent UTIs than children with isolated VUR [540]. Bladder and bowel dysfunction is common in toilet-trained

children presenting with UTI with or without primary VUR. A subgroup meta-analysis also shows that functional constipation is common in these children, with almost every third child affected by it. It was also found that the presence of both BBD and VUR doubles the risk of recurrence of UTI; hence, all children presenting with UTI should be carefully evaluated for presence of BBD and managed accordingly [980].

In LUTD, VUR is often low-grade and US findings are normal, and there is no indication for performing VCUG in all children with LUTD, but the presence of febrile infections should be meticulously investigated. The co-existence of LUTD and VUR means it would be better to do a test covering both conditions, such as a 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.

*3.15.3 **Disease management***

There are two main treatment approaches: conservative (non-surgical and surgical).

3.15.3.1 Non-surgical therapy

The objective of conservative therapy is prevention of febrile UTI. It is based on the understanding that:

- Vesicoureteric reflux can resolve spontaneously, mostly in young patients with low-grade reflux. Renal scarring is also a significant risk factor for breakthrough UTI and could be used to determine those at risk of symptomatic VUR persistence [981];
- 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 [982];
- Vesicoureteric reflux is very unlikely to damage the kidney postnatally when patients are free of infection and have normal LUT function;
- There is no evidence that small scars even bilateral 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 and bowel rehabilitation in those with LUTD [704, 979, 983-985];
- Circumcision during early infancy may be considered as part of the conservative approach as it is effective in reducing the risk of infection in normal children [986].

3.15.3.1.1 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. Vesicoureteral reflux increases the risk of febrile UTI and renal scarring especially when in combination with LUTD. Constipation in VUR patients with UTI is common and the prevelence can reach 27%. Assessment and management of all toilet trained children presenting with UTI should be a part of conservative follow-up [980]. During the conservative management of high-grade infant reflux, spontaneous downgrading and resolution of VUR is more likely. However this also depends on gender, breakthrough UTI, renal damage type and bladder dysfunction. Practical scoring systems for making decisions on further treatment, surveillance, prophylaxis or surgical intervention exist [987]. Conservative management should be dismissed in all cases of febrile breakthrough infections, despite prophylaxis, and intervention should be considered.

3.15.3.1.2 Continuous antibiotic prophylaxis

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 [988-990]. Trials show the benefit of CAP is none or minimal in low-grade reflux. Continuous antibiotic prophylaxis is useful in patients with grade III and IV reflux in preventing recurrent infections but its use in preventing further renal damage is not proven. For VUR children receiving CAP, younger age at the initial diagnosis of UTI (≤ 12 months), bilateral VUR, and BBD are independent risk factors for the occurrence of break through UTIs [991]. Toilet-trained children and children with LUTD derive better benefit from CAP [990, 992-996]. 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 [997-1000]. Additional review of the RIVUR data based on a risk classification system defines a high-risk group (uncircumcised males; presence of BBD and high grade reflux) who would benefit from a antibiotic prophylaxis significantly. In the context of management with CAP in VUR patients, this should be viewed as a spectrum and a shift from 'absolute' CAP in dilated VUR towards a 'selective' risk-based approach and should be supported

[1001]. 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.

The literature generaly consists of prescribing daily antibiotics at one quarter to one half the regular therapeutic dose. Trimethoprim-sulfamethoxazole, amoxicilin and nitrofurantoin are the most commonly used CAP agents. A child with a UTI and significant VUR can still be recommended to be treated conservatively at first, with surgical care reserved for incompliance for CAP, breakthrough UTIs under CAP and significant VUR that persists of long-term follow-up [991, 1002].

Determination of optimal timing to discontinue CAP is controversial however patients administered CAP for less than a year after the last febrile UTI and those with bilateral VUR are likely to have more frequent recurrence. Administration of CAP more than one year after the last febrile UTI can potentially be beneficial to avoid recurrent UTIs [1003]. 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 should be tailored for each VUR case together with the patient and caregivers. It is strongly advised that the advantages and disadvantages should be discussed in detail and easy/early access to healthcare during febrile UTIs should be taken into consideration.

One of the biggest concerns of CAP for patients, caregivers and physicians is the long-term effects of CAP. As a secondary outcome of the RIVUR study, TMP-SMZ prophylaxis for two years did not reveal any adverse effect on complete blood count (CBC), serum electrolytes and creatinine and such routine laboratory tests in otherwise healthy children is not mandatory [1004]. Impact of long-term CAP on gut microbiota in children with VUR is contraversial and requires more research [1005, 1006].

Continuous antibiotic prophylaxis, for prevention of UTIs in symptomatic VUR, which diagnosed during the work-up of antenatal hydronephrosis, is recommended in the first year of life. However, the current literature remains unclear whether infants diagnosed with asypmtomatic VUR during the antenatal hydronephrosis work-up will also benefit from CAP [1007].

Recommendations	**Strength rating**
Initially treat all symptomatic patients diagnosed within the first year of life with continuous antibiotic prophylaxis, regardless of the grade of reflux or presence of renal scars.	Weak
Offer immediate, parenteral antibiotic treatment for febrile breakthrough infections.	Strong
Initially manage all children presenting at age one to five years conservatively.	Strong
Offer close surveillance without antibiotic prophylaxis to children presenting with lower grades of reflux and without symptoms.	Strong
Ensure that a detailed investigation for the presence of lower urinary tract dysfunction (LUTD) is done in all and especially in children after toilet-training. If LUTD is found, the initial treatment should always be for LUTD.	Strong

3.15.3.2 Surgical treatment

Surgical treatment can be carried out by endoscopic injection of bulking agents or ureteral re-implantation.

3.15.3.2.1 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 supports the distal ureter, lengthens the submuscosal tunnel 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. Reflux timing during VCUG can be used to predict the success rate of endoscopic treatment, since reflux occuring only during the voiding phase has a higher success than filling phase VUR [1008].

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 (D/HA) (Deflux™, Dexell®) and more recently polyacrylatepolyalcohol copolymer hydrogel (PPC) (Vantris®) [1009, 1010].

Although the best results have been obtained with PTFE [1011], due to concerns about particle migration, PTFE has not been approved for use in children [1012]. 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. Injection can be performed under the ureteric orifice to create a volcanic appearance or by using a hydrodistension technique to the ureteric orifice followed by injection to the intramural ureter.

In a meta-analysis [1013] 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. The required injection volume of PPC and D/HA to achieve the same success rate can differ between agents and is generally less for PPC [1014, 1015].

Ureteral diameter ratio is a relatively recent objective measurement and appears to be a new predictive tool for clinical outcome and success after endoscopic injection of VUR [1016].

Obstruction at UVJ (UVJO) may happen in the long term follow-up after endoscopic correction of reflux. Patients with high-grade reflux and dilated ureters are at risk of late obstruction. Although in the short term (3-6 months) follow-up success rates and UVJ obstruction seems to be comparable in the long run, it is significantly more common when polyacrylate-polyalcohol copolymer is used as bulking substance [1017-1020]. The ureteral reimplantation following a failed endoscopic surgery is more challenging after PPC and distal ureter can not be preserved and requires excision due to fibrosis [1015]. Although ureteral fibrosis or inflamatory changes following Vantris injection causing UVJO has been shown to be similar to other injection materials, still PPC demonstrates a higher obstruction rate [1021].

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%) [1022]. Longer follow-up studies are needed to validate these findings.

High grade VUR in infants can be treated with injection therapy and the resolution rate is higher than that of prophylaxis. However, this can not be recommended for all high grade infants with VUR since not only all are symptomatic and but also resolution or downgrading can be achieved at favourable conditions such as unilaterality, grade IV and low residual urine [1023, 1024].

3.15.3.2.2 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%) [1025].

The most popular and reliable open procedure is cross trigonal re-implantation described by Cohen [1019]. The main concern with this procedure is the difficulty of accessing the ureters endoscopically, if needed, when the child is older. Alternatives are suprahiatal re-implantation (Politano-Leadbetter technique) and infrahiatal re-implantation (Glenn-Anderson technique). If an extravesical procedure (Lich-Gregoir) is planned, cystoscopy should be performed pre-operatively to assess the bladder mucosa and the position and configuration of the ureteric orifices. In bilateral reflux, an intravesical anti-reflux procedure may be considered, because simultaneous bilateral extravesical reflux repair carries an increased risk of temporary post-operative urine retention [1026]. Overall, all surgical procedures offer very high and similar success rates for correcting VUR.

3.15.3.2.3 Laparoscopy and robot-assisted

There have been a considerable number of case series of transperitoneal, extravesical and pneumovesicoscopic intravesical ureteral re-implantation, which have shown the feasibility of the techniques. A recent systemic review and meta-analysis comparing laparoscopic extravesical (LEVUR) vs. transvesicoscopic ureteral reimplantation (TVUR), revealed both to be good alternatives in terms of success and complication rates. Laparoscopic extravesical ureteral reimplantation is generally biasly preferred for unilateral low grade cases and therefore appears to have a higher success and shorter hospital stay [1020].

Various anti-reflux surgeries have been performed with the robot and the extravesical approach is the most commonly used. Although initial reports give comparable outcomes to their open surgical counterparts in terms

of successful resolution of reflux, recent meta-analysis of results of Robotic-Assisted Laparoscopic Ureteral Reimplantation (RALUR) are within a wide range of variation and on average they are poor compared to open surgery. Operative times, costs and post-operative complications leading to secondary interventions are higher with RALUR but post-operative pain and hospital stay is less compared to open surgery [1027-1030].

In addition, 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 caregivers in centres where there is established experience [986, 1031-1039]. Older children with complex anatomy and/or following a failed injection or open reimplant, can specifically benefit from RALUR since the robotic approach can facilitate the exposure. RALUR can be performed uni or bilateral, although caution is advised in bilateral cases due to the risk of transient retention [1028].

De novo hydronephrosis up to 30% can occur after extravesical RALUR and behave similarly to open ureteral reimplantation which is self resolving in the overwhelming majority of cases [1040].

3.15.4 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.	3
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.	4
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 reimplantation is better than endoscopic correction for higher grades of reflux, whereas satisfactory results can be achieved by endoscopic injection for lower grades.	3
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.	4

Recommendations	**Strength rating**
Offer reimplantation or endoscopic correction to patients with frequent breakthrough infections.	Weak
Offer reimplantation to patients with persistent high-grade reflux and endoscopic correction for lower grades of reflux.	Strong
Offer surgical repair to children above the age of one presenting with high-grade reflux and abnormal renal parenchyma.	Weak
Offer surgical correction, if parents prefer definitive therapy to conservative management.	Strong
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. Refer to Table 3 for risk factors and follow-up.	Weak
In high-risk patients who already have renal impairment, a more aggressive, multi-disciplinary approach is needed.	Strong

Table 3: 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	Reimplantation has better results than endoscopic surgery	Post-operative VCUG on indication only; follow-up of kidney status until after puberty
Moderate	Symptomatic male or female patients before toilet-training, with high-grade reflux and abnormal kidneys	CAP is the initial treatment. Intervention may be considered in cases of BT infections or persistent reflux	Spontaneous resolution is higher in males	Follow-up for UTI/ hydronephrosis; full re-evaluation after 12-24 months
Moderate	Asymptomatic patients (PNH or sibling) with high-grade reflux and abnormal kidneys	CAP is the initial treatment. Intervention may be considered in cases of BT, infections or persistent reflux		Follow-up for UTI/ hydronephrosis; full re-evaluation after 12-24 months
Moderate	Symptomatic male or female patients after toilet-training, with high-grade reflux and normal kidneys with LUTD	Initial treatment is always for LUTD with CAP. Intervention may be considered in cases of BT infections or persistent reflux	In case of persistent LUTD, despite urotherapy, intervention should be considered. The choice of intervention is controversial	Follow-up for UTI and LUTD, kidney status; full re-evaluation after successful urotherapy
Moderate	Symptomatic male or female patients after toilet-training with low-grade reflux, abnormal kidneys with or without LUTD	Choice of treatment is controversial. Endoscopic treatment may be an option. LUTD treatment should be given if needed		Follow-up for UTI, LUTD, and kidney status until after puberty
Moderate	All symptomatic patients with normal kidneys, with low-grade reflux, with LUTD	Initial treatment is always for LUTD with or without CAP		Follow-up for UTI and LUTD
Low	All symptomatic patients with normal kidneys, with low-grade reflux, with no LUTD	No treatment or CAP	If no treatment is given, parents should be informed about risk of infection	Follow-up for UTI
Low	All asymptomatic patients with normal kidneys with low-grade reflux	No treatment or CAP in infants	If no treatment is given, parents should be informed about risk of infection	Follow-up for UTI

BT = breakthrough; CAP = continuous antibiotic prophylaxis; LUTD = lower urinary tract dysfunction; PNH =

prenatal diagnosed hydronephrosis; UTI = urinary tract infection; VCUG = voiding cystourethrography.

3.16 Urinary stone disease

*3.16.1 **Epidemiology, aetiology and pathophysiology***

Paediatric stone disease is an important clinical problem in paediatric urology practice. Due to its recurrent nature, every effort should be made to discover the underlying metabolic abnormality so that it can be treated appropriately. The main goal is to maintain a stone-free state with close follow-up, although it may not be possible in some circumstances (e.g. oxalosis or nephrocalcinosis).

Bladder stones are still common in under-developed areas of the world and are usually ammonium acid urate and uric acid stones, strongly implicating dietary factors [1041, 1042]. Hypocitraturia is the most common metabolic abnormality, followed by hypercalciuria [1043]. Patients with augmented bladder constitute another important group with a risk of up to 15% [1044].

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 countries. However, recent epidemiological studies have shown that the incidence of paediatric stone disease is also increasing in the Western world [1045-1047]; especially in girls, Caucasian ethnicity, African Americans and older children [1048]. More than 70% of stones in children contain calcium oxalate, while infectious stones are found more frequently in younger children [1049]. The risk for stone recurrence among childhood stone formers has been reported to be 35-50%. No sex differences could be found regarding the stone recurrence risk [1050, 1051].

*3.16.2 **Classification systems***

Urinary stone formation is the result of a complex process involving genetic, dietary, metabolic, anatomical factors and presence of infection.

3.16.2.1 Calcium stones

Calcium stones are usually made from calcium oxalate or calcium phosphate. Super-saturation of calcium (hypercalciuria) and oxalate (hyperoxaluria) or decreased concentration of inhibitors, such as citrate (hypocitraturia) or magnesium (hypomagnesemia) play a major role in the formation of calcium oxalate stones. Higher super-saturations of calcium oxalate were shown to be associated with multiple stone disease [1052].

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 [1053].
Hypercalciuria can be classified as either idiopathic or secondary. Idiopathic hypercalciuria is diagnosed when clinical, laboratory, and radiographic investigations fail to delineate an underlying cause leading to hypercalcaemia. Urinary calcium may increase in patients with high sodium chloride intake.
Secondary hypercalciuria occurs when a known process produces excessive urinary calcium. In secondary 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) [1054].

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 [1053, 1054]. If the follow-up ratios are normal, then no additional testing for hypercalciuria is needed.

However, if the ratio remains elevated, a timed 24-hour urine collection should be obtained and the calcium excretion calculated. The 24-hour calcium excretion test is the standard criterion for the diagnosis of hypercalciuria. If calcium excretion is higher than 4 mg/kg/day (0.1 mmol/kg/day), the diagnosis of hypercalciuria is confirmed and further evaluation is warranted: levels of serum bicarbonate, creatinine, alkaline phosphatase, calcium, phosphorus, magnesium, pH, and parathyroid hormone. Freshly voided urine should be measured for pH [1053-1055]. In addition to calcium, the 24-hour urine analysis should also include phosphorus, sodium, magnesium, uric acid, citrate and oxalate.

Initial management is always to increase fluid intake and urinary flow. Dietary modification is a mandatory part of effective therapy. The child should be referred to a dietician to accurately assess 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 [1056]. A brief trial of a low calcium diet can be carried out to determine if exogenous calcium intake and/or calcium hyperabsorption is contributing to high urinary calcium. Any recommendation to restrict calcium intake below the daily needs of the child should be avoided. Moreover, low calcium intake is a risk factor for stone formation [1057] (LE: 3).

Hydrochlorothiazide and other thiazide-type diuretics may be used to treat idiopathic hypercalciuria, especially with calcium renal leak, at a starting dosage of 0.5-1 mg/kg/day [1058-1061] (LE: 3). In long-term use of thiazide-type diuretics, a decrease in hypocalciuric effect may be seen after the third month and may cause hypokalemia, hypocitraturia, hyperuricaemia and hypomagnesaemia. Therefore, control of blood and serum values should be performed in regular intervals. Citrate therapy is also useful if citrate levels are low or if hypercalciuria persists, despite other therapies [1058, 1062] (LE: 4).

Hyperoxaluria: Only 10-15% of oxalate is dietary. The average child excretes less than 50 mg (0.57 mmol)/1.73 m2/day [1063-1065], while infants excrete four times as much. Hyperoxaluria may result from increased dietary intake, enteric hyperabsorption (as in short bowel syndrome) or an inborn error of metabolism.

In rare primary hyperoxaluria, one of the two liver enzymes that play a role in the metabolism of oxalate may be deficient. With increased deposition of calcium oxalate in the kidneys, renal failure may ensue, resulting in deposition of calcium oxalate in other tissues (oxalosis). The diagnosis is made upon laboratory findings of severe hyperoxaluria and clinical symptoms. The definitive diagnosis requires a liver biopsy to assay the enzyme activity. Patients with primary hyperoxaluria exhibit a substantial clinical burden such as renal stones, UTIs and pain, requiring frequent healthcare resource use [1066].

Other forms of hyperoxaluria, as mentioned earlier, may be due to hyperabsorption of oxalate in inflammatory bowel syndrome, pancreatitis and short bowel syndrome. Yet, the majority of children have 'mild' (idiopathic) hyperoxaluria, with only mildly elevated urine oxalate levels in these cases. The treatment of hyperoxaluria consists of the promotion of high urine flow, restriction of dietary oxalate and regular calcium intake. Pyridoxine may be useful in reducing urine levels, especially in primary hyperoxaluria. Citrate administration increases inhibitory urine activity [1058, 1067] (LE: 4).

Hypocitraturia: Citrate is a urinary stone inhibitor. It 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 urinary citrate of less than 320 mg/day (1.5 mmol/day); this value must be adjusted for children depending on body size [1068-1070]. 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 [1069, 1071]. The urine calcium-to-citrate ratios were higher in recurrent calcium stone forming children than solitary formers [1068, 1072].

The restoration of normal citrate levels is advocated to reduce stone formation, although there are few relevant studies in children. Hypocitraturia is treated by potassium citrate at a starting dose of 1 mEq/kg, given in two divided doses [1059] (LE: 3). The side effects of potassium citrate are very rare and most of the time they include non-specific gastrointestinal complaints. Potassium citrate should be used with caution in hyperkalemic and chronic renal failure conditions.

3.16.2.2 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 [1058]. The formation of uric acid stones is mainly dependent on the presence of an acidic urinary composition. Uric acid dissociation and solubility is strongly reduced at a 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 [1058]. In patients who failed conservative measures with sustaining hyperuricosuria and hyperuricemia, stone recurrences or myeloproliferative diseases, allopurinol (10 mg/kg) may be used. This medication may cause several drug reactions (rash, diarrhoea, eosinophilia) and should be cautiously used in chronic renal failure patients.

3.16.2.3 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 cysteine precipitation beginning at pH levels < 7.0. Other metabolic conditions, such as hypercalciuria, hypocitraturia and hyperuricosuria, may accompany cystinuria, so leading to the formation of mixed-composition stones. Cystine stones are faintly radiopaque and may be difficult to visualise on regular radiograph studies. They are also hard in texture and more difficult to disintegrate by extracorporeal shockwave lithotripsy (SWL). Cystinuric patients present with larger stones at the time of diagnosis, higher new stone formation rates, and are at higher risk of surgery [1073].

The medical treatment for cystine stones aims to reduce cystine saturation in urine and increase its solubility. The initial treatment consists of maintaining a high urine flow and the use of alkalinising agents, such as potassium citrate to maintain urine pH at above 7.0 (better above 7.5). If this treatment fails, the use of α-mercaptopropionyl glycine or D-penicillamin may increase cystine solubility and reduce cystine levels in urine and prevent stone formation. Side effects of these drugs are mostly mild and include gastrointestinal complaints (alterations in taste and odour), fever and rash, however they can be associated with severe side effects, such as bone marrow depression, nephrotic syndrome and epidermolysis [1074].

3.16.2.4 Infection stones (struvite stones)

Infection-related stones constitute nearly 5% of urinary stones in children, though incidence increases over 10% in younger ages [1075] and in non-endemic regions [1049, 1076]. 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.

3.16.3 ***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 [1077, 1078].

3.16.3.1 Imaging

Generally, US should be used as a first approach. 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 [1079-1081]. 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 radiograph. Low dose protocols have also been developed with the goal of reducing radiation dose with adequate image quality [1082]. Intravenous pyelography is rarely used in children, but may be needed to delineate the caliceal anatomy prior to percutaneous or open surgery.

3.16.3.2 Metabolic evaluation

Due to the high incidence of predisposing factors for urolithiasis in children and high stone recurrence rates, every child with a urinary stone should be given a complete metabolic evaluation [1041, 1074, 1083-1085]. A

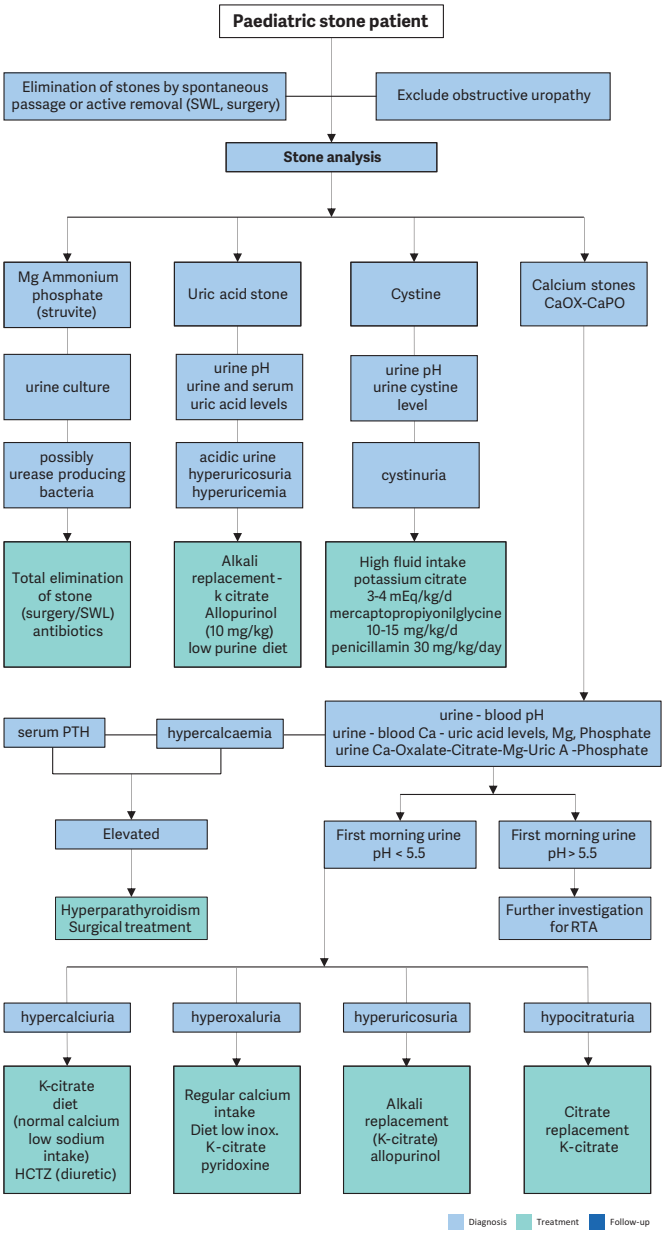
limited urinary metabolic evaluation (24-h calcium, 24h-citrate, and 24h-oxalate and low urinary volume) is able to detect the vast majority of clinically significant metabolic abnormalities [1086]. However, most of the time collections are inadequate and have to be repeated [1087].

Metabolic evaluation includes:

- family and patient history of metabolic problems and dietary habits;
- analysis of stone composition (following stone analysis, metabolic evaluation can be modified according to the specific stone type);
- electrolytes, blood/urea/nitrogen (BUN), creatinine, calcium, phosphorus, alkaline phosphatase, uric acid, total protein, carbonate, albumin, and parathyroid hormone (if there is hypercalcaemia);
- spot urinalysis and urine 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 11 provides an algorithm of how to perform metabolic investigations in urinary stone disease in children and how to plan medical treatment accordingly.

Figure 11: Algorithm for metabolic investigations in urinary stone disease in children



Ca = calcium; HCTZ = hydrochlorothiazide; Mg = magnesium; Ox = oxalate; PTH = parathyroid hormone; SWL = extracorporeal shockwave lithotripsy; RTA = renal tubular acidosis; Uric A = uric acid.

3.16.3.3 Urolithiasis in infants

Approximately 9 to 23% of paediatric urolithiasis patients are under one year old. Infantile urolithiasis appears to be a separate entity since the aetiology and the clinical course of the disease is different than in other age groups. A study on 2,513 children with urolithiasis demonstrated that microlithiasis (< 3mm) in infants should be differentiated from other age groups since the majority of them (85%) resolve spontaneously after one year of follow-up. It has also been shown that underlying metabolic abnormality is different than in older children. In this specific age group, calcium oxalate stones are not as common as in older age groups, whereas ammonium acid urate stones are more common [1042, 1088]. However if the stone size increases or the patient becomes symptomatic during follow-up, it should be treated appropriately. Another study found that only 15% of infantile urolithiasis required intervention after one year follow-up and the only predictor for intervention was the size of the stone [1089]. Two other studies concluded that stone size larger than 4.5 mm and 5 mm in infants are more likely to require intervention [1090, 1091]. Therefore observation should be the primary option for the majority of the infantile urolithiasis; if the patient becomes symptomatic or there is an increase in size, intervention can be discussed.

If an intervention is planned, SWL, RIRS or PCNL can be offered depending on the characteristics of the stone and the patient. All treatment modalities were found to be feasible with high success rates in infants [1092-1094].

3.16.4 ***Management***

Adequate fluid intake and restricting the use of salt within daily allowance range are the general recommendations besides the specific medical treatment against the detected metabolic abnormalities. With the advance of technology, stone management has changed from open surgical approaches to endoscopic techniques that are less invasive. Deciding on the type of treatment depends on the number, size, location, stone composition and the anatomy of the urinary tract [1084, 1095, 1096]. Expectant management is the initial management in children with asymptomatic small size stones (< 4-5 mm) with a possibility of spontaneous clearance. A recent study in a paediatric population showed that stone size > 6.7mm and haematuria were negative predictors for spontaneous stone passage [1097]. There is no consensus on the size of stones for different ages eligible for clearance and the duration of conservative follow-up. Adult literature reveals the benefits of medical expulsive therapy (MET) using α-blockers. Although, experience in children is limited showing different results [1098], a 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 [1085, 1099]. Stone size, and ureteral wall thickness were found to be highly predictive for MET success; patient age, BMI, stone density and degree of hydronephrosis had no predictive value in this aspect [1100]. Another RCT in the age group of 6-14 years comparing the effectivity of Silodosin, Tamsulosin and placebo as MET for distal ureteric stones less than 1 cm revealed higher stone expulsion rate for Silodosin (89.3%), compared to Tamsulosin (74.5%) and placebo (51.8%) in children [1101]. A Cochrane review including 125 children from 1-18 years old with Ca-containing idiopathic nephrolithiasis showed that oral potassium citrate may reduce recurrence after SWL; however a substantial number of children stopped medication due to adverse events [1102].

Currently, most paediatric stones can easily be managed by SWL, RIRS or PCNL. Only a small portion of children with anatomical abnormalities may require other types of surgical intervention (open, robotic, laparoscopic). All attempts must be made to completely remove all stones since post-operative residual fragments pass spontaneously in only 20-25% of cases [1103, 1104]. A congenital obstructive uropathy should be managed together with stone removal therapy to prevent recurrence.

3.16.4.1 Extracorporeal shockwave lithotripsy

Many reports confirm that SWL can be performed in children with no suspicion of long-term morbidity of the kidney [1105-1112].

The mean number of shockwaves for each treatment is approximately 1,800 and 2,000 (up to 4,000 if needed) and the mean power settings vary between 14 kV and 21 kV. Recently, two separate RCTs compared the outcomes of low vs. intermediate frequency during SWL and found no significant difference [1113, 1114]. 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 [1095, 1115, 1116]. 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 [1117] (LE: 2b). The general perception of paediatric SWL requiring anaesthesia has been challenged by a study showing that SWL without anaesthesia can be performed safely with comparable success rates in co-operative children > 9 years of age [1118].

Stone-free rates are significantly affected by various factors. Regardless of the location, as the stone size increases, the stone-free rates decrease and retreatment 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 [1095, 1115, 1116, 1119-1123]. Previous history of open surgery also decrease the success of SWL [1124].

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% [1123, 1125, 1126].

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 [1123, 1126-1128].

The type of machine used significantly influences 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 [1121].

Although stenting does not affect stone clearance, overall complication rates are higher and hospital stay is longer in the unstented patient with larger stones [1121, 1123]. 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 [1074, 1120].

The Hounsfield Unit (HU) of stone on non-contrast 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 [1104] and 1,000 [1129]. Two nomogram studies revealed male gender, younger age, smaller stone size, single stone, non-lower pole localisation and negative history for previous intervention are favourable factors for stone clearance in paediatric SWL [1130, 1131]. A comparative study reported that these two nomograms are independent predictors of stone-free rate following SWL in paediatric patients [1132]. A systematic review confirmed that those two nomograms have equal value in predicting outcomes of SWL in children [1133]. Although, the invention of miniaturised endoscopic instruments seems to reduce the importance and popularity of SWL, it has the advantage of not carrying the risk of certain complications related to endoscopic surgeries and also with less post-operative emergency visits, pain and anaesthetic sessions [1134, 1135]. 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 [1136]. However, every effort should be made to sterilise the urine before performing SWL, ureteroscopy (URS), or percutaneous nephrolithotomy (PCNL).

3.16.4.2 Percutaneous nephrolithotomy

Shockwave lithotripsy is the first choice for treating most renal paediatric stones. However, percutaneous renal surgery should be used for larger and complex stones. Pre-operative evaluation, indication and surgical technique are similar in children and adults. In most cases, percutaneous nephrolithotomy (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 (miniPCNL, ultraminiPCNL, superminiPCNL and microperc) means that PCNL can be used in children. Miniaturised PCNL has several advantages compared to standard PCNL, such as a smaller skin incision, single-step dilation and sheath placement, good working access for paediatric instruments, variable length, and lower cost [1136-1138].

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 [1139-1144]. The mean post-operative hospital stay is between one to four days and is much shorter than open surgery [1145]. The less invasive nature of this technique has made it superior to open surgery for treating renal stones in children [1146-1153].

The most frequently reported complications of PCNL in children are bleeding, post-operative fever or infection, and persistent urinary leakage. Bleeding requiring transfusion is reported in less than 10% [1149, 1152, 1154-1157] and is closely associated with stone burden, operative time, sheath size and the number of tracts [1149, 1150, 1158]. In recent studies, post-operative infectious complications, such as fever with or without documented UTI, are reported as less than 15% [1149, 1152, 1154, 1155, 1157, 1159] and the origin of fever is not always found to be the infection. Due to the smaller size of the probes, laser energy is easier to use in smaller instruments and is more useful for paediatric cases [1139, 1160-1162].

Using high power laser (> 40 W) during PCNL is feasible and may be helpful in the treatment of staghorn stones [1163], but it should be kept in mind, that increased temperatures inside the smaller paediatric kidney might lead to tissue damage, which has been shown in simulation models [1164].

With the availability of smaller size instruments, miniaturised PCNL ('miniperc') through a 13F or 14F sheath [1138, 1159, 1165] as well as ultramini-PCNL (UMP) through 12F sheaths [1166] have become possible, with decreased transfusion rates [1159]. The mini- and supermini- PCNL (SMP) were shown to have higher efficacy with low complication rates (< Clavien grade 3b) which were deemed to be a safe alternative to SWL by some authors [1146, 1167]. In this study, 108 children under 12 years old with single stone (10-20mm) in the renal pelvis or calyces were randomised into two groups; either miniPCNL or SWL. Stone-free rate (SFR) after single session was significantly higher for PCNL (88.9%) compared to SWL (55.6%) [1146]. After second and third sessions, SWL success increased to 88.8% [1168]. The complication rates were 22.2% in PCNL and 14.8% in SWL without statistical significance.

The SMP was shown to be advantageous over mini-PCNL in terms of complications with similar stone-free rates [1168, 1169]. This miniaturisation has been further developed into the technique of 'micro-perc' using a 4.85F 'all-seeing needle'. This technique enables the stone to be fragmented by a laser *in situ* and left for spontaneous passage [1170]. A study revealed that microperc provides a similar SFR with similar complication rates and a lower additional treatment rate compared with SWL in the treatment of kidney stone disease in children [1171]. For stones 10-20 mm, micro-PCNL was shown to have comparable results, with less bleeding, compared to mini-PCNL [1147] and similar outcomes with less anaesthetic sessions compared to RIRS [1153]. As experience has accumulated in adult cases, new approaches have started to be applied in children, including tubeless PCNL. This technique has been used in uncomplicated surgery for stones < 2 cm, with patients left either with an indwelling catheter or double J stent in the ureter [1156, 1172] or totally tubeless [1173]. Moreover, use of US for establishment of access is gaining popularity [1148, 1151, 1174].

Traditionally, PCNL in children is performed in prone position. Another trend in the literature is the performance of PCNL in flank-free modified supine position in children [1174, 1175]. The proposed advantages are shorter operative time and enabling a simultaneous ureteroscopic procedure without changing the position of the patient. In a recent study, 55 paediatric patients with kidney stones who underwent UMP were randomised into two groups; flank-free modified supine position (FFMS) versus prone position. Stone free rates and complications rates were similar but the operative time was found to be shorter for supine position [1176].

For post-operative pain management, two randomised controlled trials showed that intercostal nerve block or erector spinae bloc were shown to provide effective post-operative analgesia in paediatric patients [1177, 1178].

3.16.4.3 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 guidewires are used and the procedure is performed using direct vision. Routine balloon dilation of the ureterovesical junction and ureteral stenting are controversial. In general, ureteric dilatation is being performed only in selected cases. There is a tendency to use hydrodilation more because it is similarly effective [1139, 1179, 1180].

Different lithotripsy techniques, including ultrasonic, pneumatic and laser lithotripsy, have all been shown to be safe and effective. Due to the smaller size of the probes, laser energy is easier to use in smaller instruments and is more useful for paediatric cases [1181].

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. The risk of post-operative hydronephrosis depends on the presence of impacted stone and ureteral injury during operation [1182]. A multi-institutional study on the use of semi-rigid ureteroscopy for ureteral calculi in children showed that the procedure is effective with a 90% SFR 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 [1179]. However, for proximal ureteral stones semi-rigid ureteroscopy is not a good first option because of higher complication and failure rates [1183].

A 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 [1184-1189]. 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 [1185, 1187]. 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 [1184, 1186-1188, 1190]. The need for additional procedures was related to stone size [1188]. Radiation exposure during URS can be minimised by using Flat Panel Detector c-Arms while simultaneously improving image quality [1191].

One RCT and four other comparative studies showed that retrograde intra-renal surgery (RIRS) had similar stone-free rates compared to SWL after three months, with fewer sessions [1134, 1192-1195]. However for stones larger than 20 mm, RIRS monotherapy has lower stone-free rates than mini-PCNL with the advantages of decreased radiation exposure, fewer complications and shorter hospital stay [1196]. In contrast, for stones between 10-20 mm, RIRS has similar success and complication rates and shorter hospital stay and low radiation exposure when compared to micro-PCNL [1197]. A recent systematic review revealed that compared with the other two treatments, PCNL had a longer operative time, fluoroscopy time and hospital stay. Shockwave lithotripsy had a shorter hospital stay, higher retreatment rate and auxiliary rate in comparison with the other two treatments. It was also shown that PCNL presented a higher efficacy quotient than the other two treatments, and RIRS had a lower efficiency than SWL and PCNL. In the subgroup analysis of paediatric patients with stone ≤ 20 mm, the comparative results were similar to those described above, except for the higher complication rate of PCNL than SWL [1198].

3.16.4.4 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 requires surgical correction. Open surgery is also necessary in children with severe orthopaedic deformities that limit positioning for endoscopic procedures.

In centres with 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 previously failed endoscopic procedures, complex renal anatomy (ectopic or retrorenal colon), concomitant UPJ obstruction or caliceal diverticula, mega-ureter, or large impacted stones. Laparoscopic stone surgery via conventional or a robot-assisted transperitoneal or retroperitoneal approach can be attempted. However, there is limited experience with these techniques and they are not routine therapeutic modalities [1199-1202].

Bladder stones in children can usually be managed by endoscopic techniques. A recent randomised trial compared transurethral cystolithotripsy versus percutaneous cystolithotripsy for bladder stones smaller than 30 mm and found similar success and complication rates with success rates more than 95% [1203]. Open surgery may also be used for very large bladder stones or for bladder stones caused by an anatomical problem.

In addition to the advantages and disadvantages of each treatment modality for the specific size and location of the stone, consideration has to be given to the availability of the instruments and the experience with each treatment modality before the choice of technique is made. Recommendations for interventional management are given in Table 4.

Table 4: Recommendations for management in paediatric stones

Stone size and localisation*	Primary treatment option	Alternative treatment options	Comment
Infant microlithiasis (<3mm, any location)	Observation	Intervention and/or medical treatment	Individualised decision according to size progression, symptoms and metabolic factors.
Staghorn stones	PCNL	Open/SWL	Multiple sessions and accesses with PCNL may be needed. Combination with SWL may be useful.
Pelvis < 10 mm	SWL	RIRS/PCNL	
Pelvis 10-20 mm	SWL/PCNL/RIRS		Multiple sessions with SWL may be needed. PCNL and RIRS have a similar recommendation grade.
Pelvis > 20 mm	PCNL	SWL/RIRS	Multiple sessions with SWL may be needed.
Lower pole calyx < 10mm	Observation or SWL	PCNL/RIRS	Stone clearance after SWL is lower than other locations.
Lower pole calyx > 10mm	PCNL	RIRS/SWL	Anatomical variations are important for complete clearance after SWL.
Upper ureteric stones	SWL	URS	Flexible scopes may be needed in case of retropulsion.
Lower ureteric stones	URS	SWL	
Bladder stones	Endoscopic (transurethral or percutaneous)	SWL/Open	Open is easier and with less operative time with large stones.

** Cystine and uric acid stones excluded.*

PCNL = percutaneous nephrolithotomy; SWL = shockwave lithotripsy; RIRS = retrograde intrarenal surgery; URS = ureteroscopy.

3.16.5 Summary of evidence and recommendations for the management of urinary stones

Summary of evidence	LE
The incidence of stone disease in children is increasing.	2
Contemporary surgical treatment is based on minimally invasive modalities. Open surgery is very rarely indicated.	2a
The term 'clinically insignificant residual fragments' is not appropriate for children since most of them become symptomatic and require intervention.	2b
Majority of the kidney stones < 3 mm in infants resolve spontaneously.	3

Recommendations	Strength rating
Use plain abdominal X-ray and ultrasound as the primary imaging techniques for the diagnosis and follow-up of stones.	Strong
Use low-dose non-contrast computed tomography in cases with a doubtful diagnosis, especially of ureteral stones or complex cases requiring surgery.	Strong
Perform a metabolic evaluation in any child with urinary stone disease. Any kind of interventional treatment should be supported with medical treatment for the underlying metabolic abnormality, if detected.	Strong
Limit open surgery under circumstances in which the child is very young with large stones, in association with congenital problems requiring surgical correction and/or with severe orthopaedic deformities that limit positioning for endoscopic procedures.	Strong
Observe infant microlithiasis, unless symptoms occur or size increases significantly.	Strong

3.17 Obstructive pathology of renal duplication: ureterocele and ectopic ureter

*3.17.1 **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).

3.17.1.1 Ureterocele

Ureterocele is four to seven 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 [1204].

3.17.1.2 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 is 1:5). Some remain asymptomatic, therefore, the true incidence is difficult to determine [1205]. 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 [1206]. The incidence of ectopic ureter is 3.5% in patients with anorectal malformations [1207].

3.17.2 Classification systems

3.17.2.1 Ureterocele

Ureterocele is a cystic dilatation that develops in the intravesical part of the submucosal ureter. The aetiology remains unclear [1208-1210]. 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 [1211]. Vesicoureteral reflux can be observed in 50% on the ipsilateral side and 20% on the contralateral side. Reflux into the ureterocele is uncommon [1212]. In the ectopic form, the upper pole is altered, frequently dysplastic, and hypo-functional or non-functional [1213]. The corresponding ureter is a mega-ureter. In the caeco-ureterocele (see definition below), the upper pole of the renal duplication is dysplastic and non-functional. Histological evaluation demonstrated that the changes represent a process of maldevelopment and may not result from infections or obstruction [1213].

3.17.2.1.1 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 mega-ureter. A contralateral renal duplication is associated with 50% of cases. Occasionally, large ureteroceles are responsible for reflux or obstruction of the contralateral upper tract.

3.17.2.1.2 Orthotopic (intravesical) ureterocele

The intravesical or orthotopic ureterocele is completely located in the bladder. Intravesical ureteroceles are mostly combined with a single kidney system and account for about 15% of cases. It is diagnosed more in older children or adults.

3.17.2.2 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 [1214]:

- 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 [1214]:

- in the posterior urethra (47%);
- in the prostatic utricle (10%);
- in the seminal vesicles (33%);
- in the vas deferens or ejaculatory ducts (10%).

*3.17.3 **Diagnostic evaluation***

3.17.3.1 Ureterocele

Prenatal US easily reveals voluminous obstructive ureteroceles [1215]. 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, however this requires a careful systematic review of the images [1216]. Magnetic resonance urography may visualise the morphological status of the upper pole and lower moieties and of the contralateral kidney as well as it can detect renal scars [1217, 1218]. Using functional MR urography, differential renal function can be assessed with low intra- and interobserver variability [1219]. Based on the prevalence of high-grade reflux, VCUG is mandatory for identifying ipsilateral or contralateral reflux and assessing the degree of intra-urethral prolapse of the ureterocele [1220]. Urethrocystoscopy may reveal the pathology in cases where it is difficult to make the differential diagnosis between ureterocele and ectopic mega-ureter.

3.17.3.2 Ectopic ureter

Most of the ectopic mega-ureters are diagnosed primarily by US. In some cases, clinical symptoms can lead to diagnosis:

- In neonates: dribbling of urine, pyuria, and acute pyelonephritis.
- In young girls: permanent urinary incontinence besides normal voiding, or significant vaginal discharge as the equivalent of incontinence; an ectopic orifice may be found in the meatal region [1221].
- 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 [1222]. In some cases, the large ectopic ureter presses against the bladder and can look like a pseudo-ureterocele [1223].

Girls who present with life-long 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 it is the most sensitive method [1224].

*3.17.4 **Management***

3.17.4.1 Ureterocele

Management is controversial with a choice between a non-operative approach, endoscopic decompression, ureteral re-implantation, partial nephroureterectomy, or complete primary reconstruction [1225-1230]. 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 caregivers' and the surgeon's preferences [1230]. When the diagnosis is made by US, prophylactic antibiotic treatment maybe indicated until a VCUG is performed.

3.17.4.1.1 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

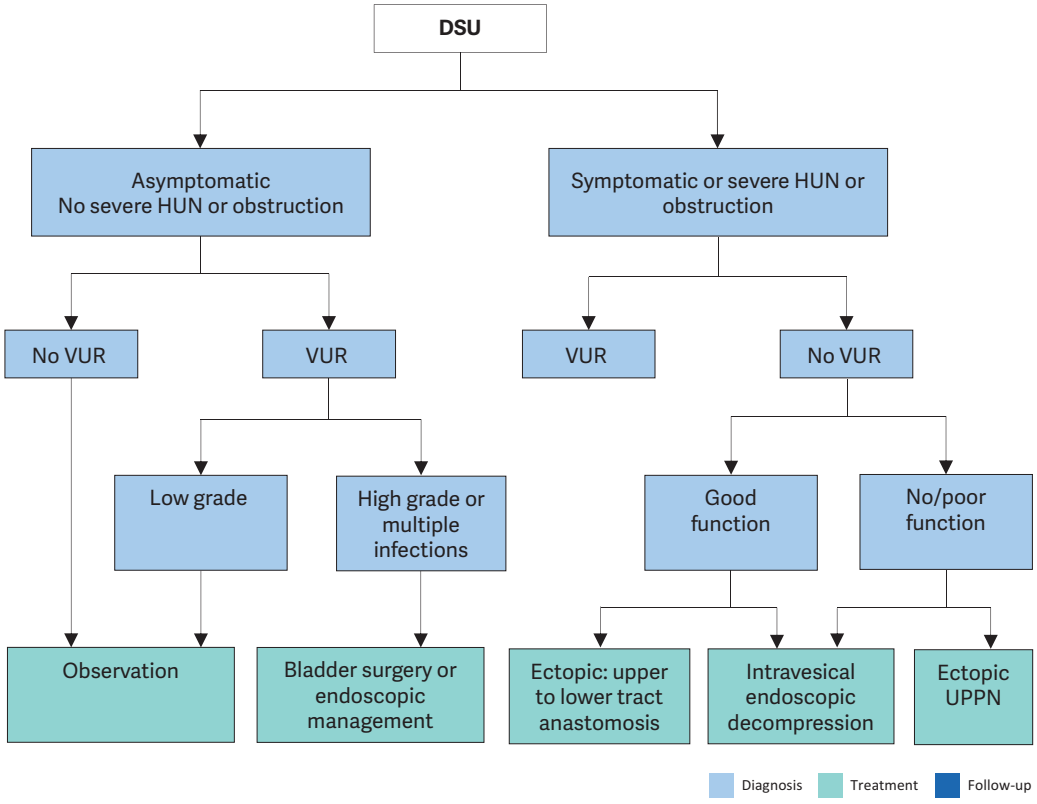
obstruction, prophylactic antibiotic treatment is given until follow-up procedures are instigated. Decompression of the dilated system facilitates later reconstructive surgery [1231, 1232].

3.17.4.1.2 Re-evaluation

Active surveillance is an option for antenatally detected ureteroceles, but long-term follow-up is necessary [1233]. Conservative treatment may be adopted in asymptomatic patients without any bladder outlet obstruction, severe hydroureteronephrosis of the ureterocele moiety or high-grade (over grade III) reflux [1230, 1234]. A meta-analysis showed that, after primary ureterocele-incision, the re-operation rate is higher in those with an ectopic ureterocele compared to those with an intravesical ureterocele [1226]. 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 [1235].

Surgery may vary from upper pole nephrectomy to complete unilateral LUT reconstruction [1229, 1236-1238]. 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) has an 80% chance of being the definitive treatment [1230, 1239]. Also a LUT approach in those with a poorly or non-functioning upper pole is an option [1240]. Today, despite successful surgery, some authors think, that surgery may not be necessary at all in some patients [1241], as less aggressive surgical treatment and non-operative management over time can achieve the same functional results [1242]. There is emerging evidence on Minimally Invasive surgical approach (laparoscopic and robot assisted) for upper pole nephrectomy with similar operating time to open surgery [1243, 1244].

Figure 12: Algorithm for the management of duplex system ureteroceles after the first 3-6 months of life [1245]



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.

3.17.4.2 Ectopic ureter

In the majority of cases, the upper pole is dysplastic and poorly functioning. There are a variety of therapeutic options, each with its advantages and disadvantages. In non-functioning moieties with recurrent infections, heminephro-ureterectomy is a definite solution. Ureteral reconstruction (ureteral re-implantation/ureteroureterostomy/ureteropyelostomy and upper-pole ureterectomy) are other therapeutic options especially

in cases in which the upper pole has function worth preserving. These procedures can be performed through an open laparoscopic or robotic assisted approach [1244, 1246-1248]. So far there is no superior approach [1249]. In patients with bilateral single ectopic ureters (a very rare condition), an individual approach depending on the sex and renal and bladder function of the patient is necessary. Usually the bladder neck is insufficient in these patients [1250].

3.17.5 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.	3

Recommendations			LE	Strength rating
Ureterocele	Diagnosis	Use ultrasound (US), radionuclide studies (mercaptoacetyltriglycine (MAG3)/ dimercaptosuccinic acid (DMSA)), voiding cystourethrography (VCUG), magnetic resonance urography, high-resolution magnetic resonance imaging (MRI), and cystoscopy to assess function, to detect reflux and rule out ipsilateral compression of the lower pole and urethral obstruction.	3	Weak
	Treatment	Select treatment based on symptoms, function and reflux as well on surgical and parenteral choices: observation, endoscopic decompression, ureteral re-implantation, partial nephroureteretomy, complete primary reconstruction. Offer, early endoscopic decompression to patients with an obstructing ureterocele.	3	Weak
Ectopic ureter	Diagnosis	Use US, DMSA scan, VCUG or MRI for a definitive diagnosis.	3	Weak
	Treatment	Treatment In non-functioning moieties with recurrent infections, heminephro-ureterectomy is a definitive solution. Ureteral reconstruction (ureteral re-implantation/ureteroureterostomy/ ureteropyelostomy and upper pole ureterectomy) are other therapeutic option especially in cases in which the upper pole has function worth preserving.	3	Weak

3.18 Disorders/Differences of sex development

3.18.1 Introduction

Formerly called 'intersex disorders', this constellation of conditions has been the subject of a consensus document in which it was decided that the term 'intersex' should be changed to 'disorders/differences of sex development' (DSD), however the original term is still used in the resolution of the Parliamentary Assembly of the Council of Europe (see below) [1251].

The new classification has arisen due to advances in knowledge of the molecular genetic causes of abnormal sexual development, controversies inherent to clinical management, and ethical issues. Controversial and negative terminology, e.g., 'pseudohermaphroditism' and 'hermaphroditism', have been renamed according to new pathophysiological insights. Furthermore, some conditions presenting with severe male genital malformation, such as penile agenesis and cloacal exstrophy, which could not previously be categorised, have now also been included. The term 'disorders/differences of sex development' is proposed to indicate congenital conditions with atypical development of chromosomal, gonadal or anatomical sex.

In addition to this, in 2017 the Parliamentary Assembly of the Council of Europe decided on a resolution termed: "Promoting the human rights of and eliminating discrimination against intersex people" [1252]. The Assembly concluded that the majority of 'intersex' people (cited verbatim from the resolution) were physically healthy and that only a few suffered from medical conditions that put their health at risk. Furthermore, they stated that the prevailing medical view at that time was that the bodies of 'intersex' children could, and should be made to conform to either a male or a female paradigm, often through surgical and/or hormonal intervention, and that this should be performed as early as possible so that these children could then be raised in the gender corresponding to their assigned sex. The Parliamentary Assembly considered that this approach involved serious breaches of physical integrity and autonomy, with many cases concerning very young children or infants who were unable to give informed consent and whose gender identity was unknown.

Therefore, the Parliamentary Assembly called on Council of Europe member states to effectively protect children's rights to physical integrity and bodily autonomy, and to empowering 'intersex' people with the following rights: Medically unnecessary sex-"normalising" surgery, sterilisation and other treatments practised on 'intersex' children without their informed consent should be prohibited, and in addition that it has to be ensured that, except in cases where the life of the child is at immediate risk, any treatment that seeks to alter the sex characteristics of the child including their gonads, genitals or internal sex organs, is deferred until such time as the child is able to participate in the decision, based on the right to self-determination, and on the principle of free and informed consent. The Panel refers to the consensus documents mentioned above as well as on the Parliamentary Assembly resolution. This chapter will focus on what is relevant for the practising paediatric urologist, as they are likely to be involved in neonates with DSD conditions.

Overall, evidence-based literature on DSD is sparse. There are no RCTs, and most studies are based on retrospective, clinical descriptive studies, or on expert opinion. An exception is made in relation to the risk of gonadal cancer, for which the level of evidence is higher [1253].
Disorders/differences of sex development can present as a prenatal diagnosis, neonatal diagnosis, or late diagnosis. Prenatal diagnosis can be based on karyotype or sonographic findings; A neonatal diagnosis is based on genital ambiguity, and a late diagnosis is usually made as a result of early or delayed puberty. In this guideline, the focus is on the neonatal presentation, where the paediatric urologist plays a more central role. There have been several publications over the last couple of decades exploring the role of prenatal corticosteroid treatment of patients with congenital adrenal hyperplasia. The Endocrine Society still proclaims their use to be restricted to research settings, and that this treatment remains experimental [1254, 1255]. For late diagnoses, we refer to endocrinology and gynaecology guidelines on precocious and delayed puberty, where paediatric urologists play a less central role [1256, 1257].

Dealing with neonates with DSD requires a multi-disciplinary approach, which should ideally include geneticists, neonatologists, paediatric and adult endocrinologists, paediatric urologists, gynaecologists, psychologists, ethicists and social workers. Each team member should ideally be experienced in DSD and a team should have treated enough patients to ensure experience.

A discrepancy is often perceived between research topics proposed by research scientists and those considered important by DSD patients [1258]. As a result of this discrepancy, collaborative networks such as the 'dsd-LIFE' consortium, have been established to include research scientists, health professionals, patient families, and support groups (available from: https://www.dsd-life.eu/home/index.html0. In the dsd-LIFE study, there is a focus on what patients and care-givers consider to be a priority, and research is then carried out around that issue. In addition, the newly established European Reference Network (ERN) covering rare endocrine conditions (Endo-ERN) considers patient participation in research and database management to be crucial (available from: https://endo-ern.eu/.

3.18.2 International Consensus Statements on DSD Management

There have been four published consensus statements in relation to the investigations and management of DSD. In general, these statements have focused on the impact of DSD on older age groups, the importance of long-term prospective multi-disciplinary, multi-centre data collection with a focus on patient reported outcomes.

The ultimate ambition is to preserve physical and psychological function in these future adults [1259]. The consensus proposal from European Society of Paediatric Radiology task force predominantly focused on imaging modalities and calls for the optimisation of US in initial and interval assessments of anatomy, with MR imaging and cystovaginography used as adjunctive modalities [1260]. The COST Action BM1303 working group 1 consensus statement from Europe raised the concern of the effects of delayed genital and gonadal surgery on physical, psychological, and sexual well-being, as well as the potential malignant risks of retained gonads. Support tools need to be developed to help guide affected families and children with a balance struck between surgery and the protection of human rights [1258]. The Canadian consensus statement broadly concurs with the above but differs slightly from their European counterparts. It suggests that sex assignment need not take place at birth, and there should be a recognition of the harms caused in the past by a paucity of information to parents, and that decisions involving surgery should take place involving a shared decision model. This consensus finally suggests that data is insufficient to determine the correct timing of surgery [1261].

*3.18.3 **Current classification of DSD conditions***

There have been a number of published updates since the International Consensus Conference on 'intersex' and its subsequent publications on the classification of the various conditions of DSD. The latest of these was published by the Global DSD Update Consortium in 2016 [1262]. As the field of DSD is continuously developing, and knowledge and viewpoints change over time, an effort has been made to to consider diversity, inclusion, and equality, and therefore representatives from support and advocacy groups continue to be invited, with an aim to focus on patient care and the best possible quality of life.

According to the international consensus in 2005, DSDs have been defined as congenital conditions within which the development of chromosomal, gonadal and/or anatomic sex is atypical. The changes that were made according to terminology are as follows:

46XX DSD – This was formerly termed female pseudohermaphrodite, over-virilisation of an XX female, and masculinisation of an XX female. In this group the vast majority is due to classic congenital adrenal hyperplasia (CAH) with various degrees of masculinisation. Among all DSD conditions together, 46XX CAH patients comprise approximately 80% cases. These conditions are extremely important since they can be potentially life threatening days after birth due to a salt-loss phenomenon, and immediate medical care is mandatory.

46XY DSD – Previously termed male pseudohermaphroditism, undervirilisation of an XY male, and undermasculinisation of an XY male. This group is often quite heterogenous and includes the partial androgen insensitivity syndrome (PAIS), as well as the complete androgen insensitivity syndrome (CAIS) formerly called testicular feminisation.

Sex chromosome mosaicism DSD (45X; 45X/46XY; 47XXY) – This cohort consists of multiple variants with the mixed gonadal dysgenesis being the most important one. Many have a normal male phenotype and others may have asymmetric genitalia. One scrotal half often contains a gonad which is likely to be a testis whereas the other side is more in keeping with a labia majora with usually no palpable gonad, which will most likely be a streak gonad.

Ovotesticular DSD – This was previously described as a 'true hermaphrodite' because of the presence of ovarian and testicular tissue co-existing in the same individual meaning. There is great variability in phenotype with uni- or bilateral undescended gonads, which can present as one ovary and one testis, or as one or two ovotestes.

Non-hormonal/non-chromosomal DSD – This cohort was introduced as well, including newborns with cloacal exstrophy where bladder and intestines are exposed through a midline mesenchymal defect resulting from the failure of the clocal membrane to retract, which then rutpures. Others in this cohort include patients with aphallia, and severe micropenis. The latter one is a normally formed penis with a stretched length of < 2.5 standard deviation below the mean [1251, 1263]. Micropenis should be distinguished from buried and webbed penis, which are usually of normal size. The length of the penis is measured on the dorsal aspect, while stretching the penis, from the pubic symphysis to the tip of the glans [1251].

*3.18.4 **Diagnostic evaluation***

3.18.4.1 The neonatal emergency

The first step is to recognise the possibility of DSD (Table 5) and to refer the newborn baby immediately to a tertiary paediatric centre, fully equipped with neonatal, genetics, endocrinology and paediatric urology units. A diagnosis of a 46XX DSD as a result of congenital adrenal hyperplasia (the most common form of DSD) should not be delayed, and represents a neonatal emergency situation due to the possibility of salt loss which can be fatal.

Table 5: 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

3.18.4.2 Family history and clinical examination
A careful family history must be taken followed by a thorough clinical examination including various laboratory tests and imaging modalities (Table 6).

Table 6: Diagnostic work-up of neonates with DSD

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
Genetics: karyotype, next-generation sequencing-based molecular diagnostics, WES
Ultrasound
Genitogram
hCG stimulation test to confirm presence of testicular tissue
Androgen-binding studies
Endoscopy

ACTH = adrenocorticotropic hormone; FSH = follicle-stimulating hormone; hCG = human chorionic gonadotropin; LH = luteinising hormone; TST = testosterone; WES = whole exome sequencing.

A thorough and standardised clinical examination in a neonate presenting with ambiguous genitalia is important. In addition to an accurate description of the ambiguous genitalia, detailed information should be documented on the palpability and localisation of the gonads. Data gathered through the various examinations described below should help the team to come to a final diagnosis. Medical photography can be useful, however this requires sensitivity and consent [1264].

Palpable gonad: If it is possible to feel a gonad, it is most likely to be a testis; this clinical finding therefore virtually excludes 46XX DSD.

Phallus: The phallus length, width, and glans width 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. A single opening has to be identified as well as a hymenal ring. Attention needs to be paid to the fusion of the labioscrotal folds as well as whether they show rugae or some discolouration.

Ultrasound can help to describe the palpated gonads or to detect non-palpable gonads [1260]. Mullerian structures like the vagina or utricular structures can be evaluated as well [1265, 1266].

Genitography can provide some more information on the urogenital sinus, especially on the exact position of the confluence. Moreover, it gives evidence of possible duplication of the vagina.

Invasive diagnostics under general anaesthesia can be helpful in some cases. During genito-cystoscopy, the urogenital sinus can be evaluated as well as the level of confluence. It allows also for evaluation of the vagina or utriculus, the possible presence of a cervix at the top of the vagina.

Laparoscopy is necessary to obtain a final diagnosis on the presence of impalpable gonads and on the presence of Mullerian structures. If indicated, a gonadal biopsy can be performed [1267, 1268].

Genetics has a increasing role in the diagnostic process of DSD. Karyotyping is usally at the beginning of the diagnostic process. Although next-generation sequencing-based molecular diagnostics and whole exome sequencing (WES) are becoming the gold standard for genetic evaluation, it may be difficult to prove variant causality or relate the genotype to the clinical presentation [1269].

These investigations will help to distinguish between various conditions of DSD, and provide a rapid diagnosis of congenital adrenal hyperplasia (CAH).

3.18.5 ***Gender assignment***

In the current climate, it goes without saying that open, honest, and complete communication with caregivers and eventually the affected person is mandatory. Educational and psychological support regarding the impact is needed for each individual to make sense of their condition, relate to their community, and establish relationships. The lack of outcome data and different preferences make it challenging to determine whether and when to pursue gonadal or genital surgery. Shared decision making is critical, combining expert healthcare knowledge and the right of a patient or caregivers to make fully informed decisions. This entails a process of education, sharing of risks/benefits, articulating the uncertainties in DSD care and outcomes in addition to providing time for the patient and family to articulate back the risks and benefits of each option. The goal of all involved should be to individualise and prioritise each patient.

However, prior published 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 considered urgent. In 2017 the Parliamentary Assembly of the Council of Europe, the European Society for Paediatric Urology (ESPU) as well as the Societies for Pediatric Urology have taken a position in the debate on surgery for DSD [1252, 1270, 1271]. In an open letter to the Council of Europe, the European Society for Paediatric Urology expressed its attitude to the abovementioned resolution and concentrated on a worrying issue dealing with medicosurgical care for children with DSD. It states that surgical interventions in children with DSD only being applied in emergency conditions is discordant with the definition of health according to the WHO, stating that health is not merely the absence of disease, but is a much broader concept, including physical, mental, and social domains. This especially applies to children, as favourable physical, social and emotional conditions are all critical factors for their optimal growth and development, which enables them to reach their full potential at an adult age. As social and emotional interactions with the parents or caregivers, being the most important adults in a young child's life, form the basis for their future, treatment of children with DSD can best be organised in a patient- and family-centred multi-disciplinary setting, in an atmosphere based on openness, commitment and trust. Physicians, who daily take care of children with a variety of congenital conditions, the same as their parents or caregivers, are committed to the current as well as the future health and well-being of all children entrusted to their care. In contrast to what is alleged in the recommendation, parents and caregivers implicitly act in the best

interest of their children and should be respected as their outstanding representatives, and should not be put aside by claiming prohibition regulations regarding the well-informed decisions they make on their behalf. Finally in a published open letter, the ESPU advocate keeping dialogue open with the professionals active in specialised centres for multi-disciplinary, patient- and family-centred care as well as with patient societies, for which the present resolution is recognised as being a solid starting base [1272].

Genital surgery
The decision to proceed with genital surgery is acknowledged to be controversial. Patient-reported outcomes from adult patients who previously underwent early genital surgery demonstrate considerable variation, with perspectives dependent on, but not limited to, diagnostic category, gender, prior experience with surgical procedures, and contact with support groups [1273].

The majority of patients who have undergone surgery rated their appearance as satisfactory from an anatomical perspective. However, functional results were found to be less satisfactory due to the development of vaginal stenosis, or diminished sensation in the clitoris or the glans penis [1274]. Clinical decision-making with respect to genital surgery in patients with a DSD should not be made wantonly, but advisedly, in a patient and family-centred multi-disciplinary setting, on a case-by-case basis. These decisions should be supported and audited by improving information on long-term outcomes, informed consent, and contact with support groups at both an individual and an institutional level.

3.18.6 ***Risk of tumour development***
The dysgenetic gonads of individuals with DSD have an increased risk of developing germ cell neoplasia *in situ* (GCNIS), previously known as carcinoma *in situ*, and overt germ cell cancer (GCC) as compared to the general population [1275]. The highest prevalence of GCC is seen in conditions characterised by disturbed gonadal development and in the presence of the Y chromosome or parts thereof (SRY & GBY encompassing regions) [1276]. In a large dsd-LIFE study the overall prevalence of neoplastic lesions was 12%. Subanalysis demonstrated a significantly higher prevalence of 36% in patients with 46 XY gonadal dysgenesis as compared with other DSD subtypes [1277]. Conversely, patients with testosterone biosynthesis disorders and androgen action disturbances (46XY DSD group) have a much lower risk (1-15%) for GCNIS development during childhood and had a limited tendency towards invasive progression of the lesions. It has been hyposthesised that a certain level of testosterone activity seems to be needed for GCNIS to progress to overt malignancy [1278, 1279]. An overview of the risks of malignancy in different subtypes of DSD is shown in Table 7.

The issue of whether gonads should be removed and the timining of such surgery remains controversial and has been altogether questioned in some forms of DSD. Patients with, for example, CAIS benefit from the presence of testicles and the resultant aromatisation of the naturally occuring testosterone to oestrogens. The risk of malignant gonadal transformation in this subcategory is low (1.5%) with cases of malignancy first appearing after the second decade of life, thus allowing for the safe deferal of gonadectomy until after puberty [1279, 1280]. This is however less clear for other subtypes of DSD, and needs to be assessed for each case according to several factors such as patient age, underlying DSD subtype and especially the presence of a Y chromosome. In such cases, the location of the gonad, possible fertility, hormonal potential of the gonad and the possibility of gonadal monitoring together with surgical/anaesthesic risks incurred by gonadectomy should be taken into account [1253, 1272]. In general, intra-abdominal gonads have to be brought down to a superficial position or pexied to the abdominal wall to allow for monitoring, self examination and ultrasound guided biopsies. High-risk gonads that fail to be brought down, or streak-like gonads should be removed based on a risk- benefit analysis, and after appropriate inter-disciplinary review [1253, 1272]. Biopsies should be reviewed by an experienced pathologist and specialised immunohistochemistry is recommended for measurement of expressions of PLAP and octamer-binding transcription factors 3 and 4, as it may be difficult to differntiate between GCNIS and delayed germ cell maturation in infants. Non-invasive markers such as serum microRNA (miRNA) for early-stage malignancy detection, have been developed, but have yet to be implemented in clinical practice [1253, 1269].

Table 7: Risk of malignancy in different subtypes of DSD (Adapted from Looijenga *et al.*, [1281])

Risk	DSD	Malignancy risk (%)
High	Gonadal dysgenesis, with Y, abdominal gonad PAIS non-scrotal gonad Frasier syndrome Denys-Drash with Y	15-35 50 60 40
Intermediate	Turner syndrome with Y 17β- hydroxysteroid dehydrogenase deficiency Gonadal dysgenesis with Y PAIS scrotal gonad	12 28 Unknown Unknown
Low	Complete androgen insensitivity syndrome Ovotesticular DSD Turner syndrome without Y	2 3 1
No	5-Alpha Reductase Deficiency Leydig cell hyperplasia	0 0

*3.18.7 **Quality of life***

In general, adult patients with DSD report good quality of life and physical health, however there is an increased risk for both somatic and psychiatric morbidities [1282]. Furthermore, a lower quality of life was reported in the domain "social relationships", which relates to personal relationships and sexual health [1283, 1284]. In addition, patients with DSD report higher levels of psychological distress and mental health problems [1285, 1286]. These elements should be included in the multi-disciplinary and holistic health care for these patients.

A person's experienced gender is a fundamental aspect of one's sense of self. Gender incongruence can occur when there is incongruence between the physical and experienced gender, and if this causes significant distress it furfills the criteria for the diagnosis gender dysphoria, according to the "Diagnostic and Statistical Manual of Mental Disorders, 5th Edition (DSM-5)" of the American Psychiatric Association [1287]. Gender dysphoria is reported low in women with CAH, CAIS and complete gonadal dysgenesis favoring female sex of rearing. Gender dysphoria is reported high in females with 5-a reductase deficiency and 17β-Hydroxysteroid dehydrogenase-3 deficiency. Gender dysphoria is reported variable in PAIS or mixed gonadal dysgenesis [1288]. Approximately 3% of DSD patients undergo a gender change after puberty, which is a small group, but larger when compared to the general population [1289, 1290].

3.18.8 Recommendations for the management of disorders/differences of sex development

Recommendations	Strength rating
Do not delay diagnosis and treatment of any neonate presenting with ambiguous genitalia since salt-loss in a 46XX CAH girl can be fatal.	Strong
Refer children to experienced centres where neonatology, endocrinology, (paediatric) urology, psychology and transition to adult care are guaranteed.	Strong
Utilise a multi-disciplinary approach and a shared decision model in patients with DSD conditions including: a. Gender assigment b. Genital surgery (in accordance with national regulations) c. Gonadectomy	Strong
Do not underestimate the significant effects on psychological and psychiatric health, quality of life, personal relationships, and sexual function in individuals with DSD.	Strong
Ensure full disclosure to patients and caregivers that the presence of a Y-chromosome in dysgenetic gonads results in a higher malignancy risk	Strong

3.19 Congenital lower urinary tract obstruction (CLUTO)

Introduction

The term congenital lower urinary tract obstruction (CLUTO) is used for intrauterine dilatation of the bladder and/or the upper urinary tract. During pregnancy the diagnosis is usually based on ultrasound examinations. There is a broad spectrum of conditions that could cause an intrauterine dilatation of the urinary tract. Congenital lower urinary tract obstruction is most commonly the result of posterior urethral valves (PUV), in approximately 60% of cases. Postpartum diagnosis, however comprises any number of anatomical and functional disorders/anomalies/malformations causing dilatation e.g. anterior urethral valves, urethral atresia/stenosis, prune belly syndrome, dilating VUR, cloacal malformation, prolapsing ureterocele, megacystis-microcolon-intestinal hypoperistalsis or megacystis-megaureter syndrome [1291].

Due to the heterogeneity and the rare spectrum of clinical manifestations of CLUTO, referral of such cases is recommended to a tertiary centre with multidisciplinary expertise in prenatal and postnatal management of obstructive uropathies [1291].

Megacystis

In the first trimester, fetal megacystis is defined as a bladder with a longitudinal diameter ≥ 7 mm. A longitudinal (craniocaudal) diameter between 7-12 mm in the first trimester is usually transient, disappearing in about 90% of cases during the second trimester. A measurement > 15 mm however, indicates CLUTO is unlikely to resolve [1291]. In the second and third trimester, megacystis is defined by an enlarged bladder failing to empty during an extended US examination lasting at least 40 minutes. Two thirds of cases are secondary to CLUTO and the remainder are associated with genetic syndromes, developmental or chromosomal abnormalities, including anorectal malformations, of which 14% were normal or had an isolated urological abnormality (e.g. VUR, Duplex system) [1291, 1292]. In a systematic review ≥ 45% of megacystis cases were shown to be associated with oligohydramnios and 15% had chromosomal abnormalities [1293]. Final diagnoses included PUV (57%), urethral atresia/stenosis (7%), prune-belly syndrome (4%), megacystis-microcolon-intestinal hypoperistalsis syndrome (MMIHS) (1%), cloacal abnormality (0.7%) and undefined pathologies (36.5%) [1293].

The prognosis of the fetus depends on the underlying pathology, the timing of diagnosis, the presence of oligo/anhydramnios and bladder volume.

*3.19.1 **Posterior urethral valves***

3.19.1.1 Epidemiology and pathophysiology

Posterior urethral valves are one of the few life-threatening congenital anomalies of the urinary tract found during the neonatal period. The risk for chronic kidney disease (CKD) is estimated to reach 32% and 20% for end-stage renal disease (ESRD), as reported in a systemic review [1294]. Up to 17% of paediatric ESRD can be attributed to PUV [1295]. An incidence of PUV of 1 in 7000-8000 live-births has been estimated [1296, 1297].

The kidneys start to produce urine at around the tenth week of antenatal life. The intrauterine obstruction leads to a decreased urine output, which could result in oligo- or anhydramnios. Amniotic fluid is necessary for normal development of the lungs and its absence may lead to pulmonary hypoplasia.

An obstruction at 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 may occasionally have multiple diverticulae.
- Nearly all valve patients have dilatation of the upper urinary tract. 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 VUR, the affected kidney functions poorly in most cases.

Secondary VUR is observed in at least 50% of patients with PUV [1298]. It is generally accepted that unilateral high grade VUR associated with ipsilateral renal dysplasia acts as a 'pressure pop-off valve', which would protect the contralateral kidney, leading to a better prognosis [1299]. Other types of pop-off mechanism include large bladder diverticulae, urinary extravasation, with or without urinary ascites and a patent urachus [1300]. Protective effects of pop-off phenomena on renal function remain however equivocal, as long-term outcomes from different studies have been discrepant, with some studies showing a protective effect [1301, 1302] while others have shown no protective benefit [1303-1305]. A possible explanation for such discrepancy could relate to differences in defining the exact nature of what constitutes a pop-off mechanism.

*3.19.2 **Classification systems of the urethral valves***

Up until today, the original classification by Hugh Hampton Young is the most commonly used classification

[1306], which described three categories: type I, type II and type III. However, today, only type I and type III are found to be obstructive. 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 [1306].

Type III: Has been found at different levels of the posterior urethra and which apparently bears no relation to the verumontanum. This obstruction attaches to the entire circumference of the urethra, with a small opening in the centre [1296].

*3.19.3 **Diagnostic evaluation***

During prenatal US screening, hydroureteronephrosis and a distended bladder are suspicious signs of a urethral valve. A thick-walled bladder seems to better predict PUV than a dilated posterior urethra ('keyhole' sign) [1307]. However, differentiation between obstructive and non-obstructive aetiologies on prenatal US is challenging, as both have a similar sonographic appearance [1308]. In the presence of increased echogenicity of the kidney, dilatation of the urinary tract and oligohydramnios, the diagnosis of a PUV should strongly be considered. Prenatal US is adequate in most of the cases (90%) [1309]. However, in some circumstances when technical ultrasound conditions are poor, fetal MRI may provide additional information [1310].

Postnatally, creatinine, blood urea nitrogen and electrolytes should be monitored closely during the first few days. Initial management includes a multi-disciplinary team involving a paediatric nephrologist. The clinician must be aware of a noteworthy association between PUV and undescended testicles (UDT) and/or inguinal hernia [1311]. Undescended testicles occurred in 12–17 % of PUV which is consistent with a 10-fold increase [1312].

A voiding cystourethrogram (VCUG) (including lateral views of the urethra during the voiding phase without a catheter *in situ*) is recommended to assess the presence of a PUV. This study is essential whenever there is a question of an infravesical obstruction, as the urethral anatomy is well outlined during voiding. The extent of posterior urethral deformity – as expressed by the posterior urethral height: width ratio – appears to correlate positively with nadir creatinine at twelve months of age [1313]. Nuclear renography with split renal function is important in assessing contributory renal function and/or scarring (DMSA or MAG3).

*3.19.4 **Management***

3.19.4.1 Prenatal treatment

Most cases of PUV are suspected prenatally [1296, 1314, 1315].

The potential for spontaneous resolution of bladder enlargement, and the timing of renal imaging are the main obstacles for prenatal intervention. As renal dysplasia is irreversible, it is important to identify those fetuses with good renal function [1316].

Prenatal interventions aim to restore amniotic fluid volume and attenuate the risk of pulmonary hypoplasia or further renal damage [1317]. Decision for prenatal intervention can be based on a staging system that is composed of renal ultrasonographic findings, amnion amount and fetal urine biochemistry [1315]. Early intervention (before the age of sixteen weeks of gestation) may be beneficial for the renal function, however making the correct diagnosis and the detection of other severe comorbidities is extremely difficult at this time point [1318]. Later interventions are mostly of benefit for lung development, but not for renal function [1319]. There are however emerging reports of interventions as early as the end of first trimester, with results pointing to a potential preservation of long-term renal function. These reports are still preliminary, the techniques used are intricate and can be associated with a higher risk of foetal demise in these very frail and tiny patients [1320-1322].

Foetal urine samples before 23 weeks of gestation (ß2-microglobulin, sodium, chloride and calcium) may be helpful to distinguish between those who could benefit from intrauterine therapy and those in whom the outcome is most likely to be compromised [1323].

Normal biochemistry; a sodium level below 100 mmol/L, a chloride value of < 90 mmol/L, calcium <8 mg/dL, and ß2-microglobulin <6 mg/L obtained in the first fetal urine sample or biochemistry that improves between two sequential samplings, the latter scenario prompting fetal intervention, was associated with high fetal survival and normal renal function at five years in a small study [1324]. The status of amnion fluid, the appearance of the kidneys as well as the fetal urine biochemistry may be helpful in counselling. Proteomic analysis of fetal urine using a 12 peptide signature expressed in fetuses who go on to develop ESRD by the age of two years, may show promise in assessing CLUTO. This should be considered as experimental.

The placing of a vesicoamniotic shunt (VAS) is a prenatal treatment designed to restore amniotic fluid cycling. There is a reported complication rate of 21-59% with dislocation of the shunt being the most common [1317]. The PLUTO-trial (randomised study) failed to show a long-term benefit on renal function by placing a VAS [1325]. A meta-analysis on interventions for CLUTO reported that VAS resulted in a higher perinatal survival rate than conservative management (57.1% vs 38.8%), with no significant differences in six to twelve month survival, two-year survival or postnatal renal function [1326]. Foetal cystoscopy with laser ablation has a high complication rate without evidence for the effectiveness of these interventions [1327]. To avoid the severe complication of the laser ablation, balloon dilation has been tried [1328]. The number of patients and designs of these studies are insufficient to yield any recommendations. Parental information is very important and the natural history of CLUTO including the postnatal outcomes with or without prenatal treatment as well as the uncertainties and/or controversies about CLUTO diagnosis and treatment should be discussed [1317].

3.19.4.2 Postnatal treatment

Bladder drainage

Following delivery, the bladder should be drained transurethrally, or suprapubically. This catheter drainage tube can then be used to perform a VCUG to confirm the diagnosis.

Valve ablation

When the medical situation of the neonate has stabilised, the next step is to perform an endoscopic valve ablation provided the urethra is accessible with available equipment. In cases were the urethra is too small, urinary diversion should be maintained until valve ablation can be performed. Small paediatric cystoscopes and resectoscopes are available either to incise, ablate or to resect the valve at the 5, 7 and/or 12 o'clock 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. Two studies demonstrated a lower urethral stricture rate using the cold knife compared to diathermy [1329, 1330]. Currently, no strong evidence exists to support the use of laser ablation of PUVs; preliminary studies on the use of Holmium YAG and Thulium lasers, show that laser fulguration is safe and effective [1331]. Within the three months following initial treatment, effectiveness of the treatment should be demonstrated either by clinical improvement (ultrasound and renal function), control VCUG or a re-look cystoscopy, depending on the clinical course [1332-1334].

Bladder neck incision

Bladder neck incision has been suggested as a means of managing secondary bladder neck obstruction [1335]. There is no current evidence which demonstrates that bladder neck incision has a role in preventing reintervention or rehospitalisation rates, and therefore cannot be recommended as a routine management option.

Vesicostomy

A vesicostomy is indicated if the child is too small to undergo endoscopic surgery, has failed endoscopic valve ablation, or has shown no clinic-biochemical improvement following valve ablation. This is an alternative to prolonged catheter drainage and has been shown to stabilise/improve the upper tracts in up to 90% cases [1336]. The most prevalent vesicostomy procedure in children was described by Blocksom and modified by Duckett [1337]. Key technical points are to ensure an adequate mobilization of the bladder dome to enable a tension-free anastomosis with the fascia and skin. Common complication following vesicostomy are stomal stenosis, mucosal prolapse, peristomal dermatitis, and bladder calculi. The risk of prolapse is usually due to an extensive bladder mobilization and due to placement of the stoma too inferior on the abdominal wall, allowing the posterior bladder wall to evert through the stoma.

High diversion

In cases where bladder drainage is insufficient to prevent recurrent infections of the upper tract, improve renal function and/or a decrease upper tract dilatation, high urinary diversion should be considered. 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 its advantages and disadvantages [1338-1340]. Diversion can delay progression to end stage renal failure [1341].

Vesicoureteric reflux is very common in PUV patients (up to 72%) and it is described bilaterally in up to 32% [1342]. A prospective observational study identified high grade VUR as an independent risk factor for developing febrile UTIs especially in the first nine months of life, therefore antibiotic prophylaxis should be considered in such patients [1343]. Furthermore, circumcision can be discussed in order to further reduce the risk of UTIs [1343]. In the aforementioned multicentred randomized controlled trial, after two years of follow-up, this study demonstrated a statistically significant effect of circumcision as an adjunct to antibiotic prophylaxis in

preventing febrile UTIs. The hazard ratio for developing a febrile UTI in the group with antibiotics alone was 10.3 (95% confidence interval: 1.3–82.5) compared with the combined prophylactic antibiotics and circumcision group.

Early administration of oxybutynin may improve bladder function as shown in one study with eighteen patients [1344], and enhances resolution of hydronephrosis and VUR as shown in a randomized controlled study of 49 patients. Oxybutynin treatment had, however no discernible effect on renal function or risk of UTI [1335]. High-grade VUR is usually associated with a poorly functioning kidney however, early removal of a non-functioning renal unit in an asymptomatic patient seems to be unnecessary. Deterioration of renal function without an anatomical obstruction and higher urine output (polyuria) may lead to an overdistension of the bladder during the night. Drainage of the bladder during the night by a catheter may be beneficial for the hydronephrosis as well as for renal function [1345, 1346]. Patients with high daytime post void residual urine volumes may benefit from clean intermittent catheterisation (CIC) [1347]. In those who do not want, or are not able to perform CIC via the urethra, the placement of a catheterizable channel is a good alternative [1348].

Clean intermittent catheterization has been shown to delay the onset of dialysis in patients with chronic kidney disease, progressing to ESRD and has also resulted in significantly better ten-year graft survival rates in transplanted patients [1349, 1350].

*3.19.5 **Follow-up***

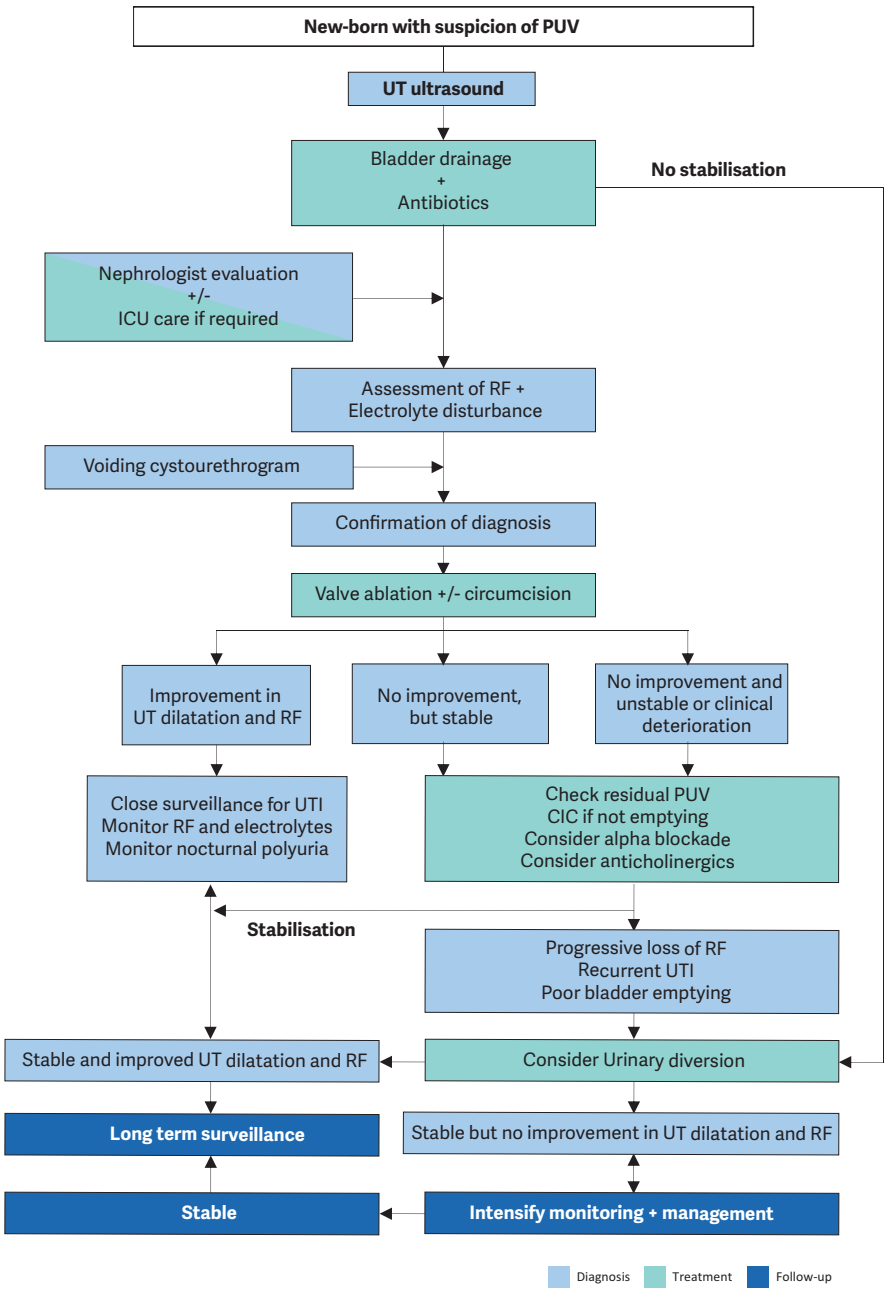
Several prognostic factors for the prediction of future renal function have been described. Different serum nadir creatinine levels are given in the literature (0.85 mg/dl – 1.2 mg/dl [µmol/L]) [1313, 1351-1354]. Renal parenchymal quantity (total renal parenchymal area) and quality (corticomedullary differentiation and renal echogenicity) on initial postnatal ultrasound also have prognostic value [1355].

Life-long monitoring of these patients is mandatory, as bladder dysfunction ('valve bladder') is common and the delay in day- and night-time continence is a significant problem [1356]. Urodynamic studies play an important role in the management of patients with valve bladder especially in those with suspicion of bladder dysfunction [1357, 1358], however there is no consensus as to optimal timing or frequency of such studies. Poor bladder sensation and compliance, detrusor overactivity and polyuria (especially at night) and their combination are responsible for bladder dysfunction. In those with bladder overactivity, anticholinergic therapy can improve bladder function. In patients with poor bladder emptying, α-blockers can be used to reduce the post-void residual [1359, 1360].

Chronic kidney disease develops in up to 65% of PUV patients and about 20% of these progress towards ESRD [1361]. Renal transplantation in these patients can be performed safely and effectively [1362, 1363]. Deterioration of the graft function is mainly related to lower urinary tract dysfunction (LUTD) [1362]. An assessment and treatment algorithm is provided in Figure 13.

There is limited data pertaining to sexual function and fertility in patients with PUV. Long-term studies have demonstrated normal erectile function and fertility potential [1364, 1365]. However, a negative influence of the individual patient's fertility has to be taken into account as these patients have a higher risk for bilateral cryptorchidism, recurrent epididymitis and ESRD [1364].

Figure 13: 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.

- **Anterior urethral valve (AUV)**

Anterior urethral valve is a semilunar or iris-like band of tissue on ventral aspect of urethra. It can be isolated, or seen in association with anterior urethral diverticulum. The aetiology of isolated AUV is speculated to be secondary to congenital urethral obstruction, malunion of glanular and penile urethra, congenital cystic dilatation of periurethral glands or ruptured distal lip of a syringocele [1366]. It can be present in the bulbous urethra, the penoscrotal junction and penile urethra. Patients may present with poor urinary stream, penile ballooning, UTI or haematuria. Anterior urethral valves were classified by Firlit depending on the presence of diverticulum and dilatation of urethra and upper tract [1367]. The diagnosis is based on a VCUG with possible findings of dilated or elongated posterior urethra, dilatation of the anterior urethra, thickened trabeculated bladder, hypertrophied bladder neck, VUR, and urethral diverticula. In doubtful cases retrograde urethrography may be helpful showing linear filling defect along the ventral wall, or it may show a dilated urethra ending in a smooth bulge or an abrupt change in the calibre of the dilated urethra on VCUG [1368].

Treatment is mainly by endoscopic valve ablation. In selected patients, temporary diversion may be considered until the child is big enough for endoscopy. Open surgery is reserved for patients with very large diverticulum

and defective spongiosum. Renal failure may develop in 22%, the risk being highest in patients with pre-treatment azotaemia, VUR and UTI [1369].

- **Anterior urethral diverticulum (AUD)**

Common postnatal presenting features of AUD are compressible ventral penile swelling, urinary postmicturition dribble, voiding difficulty, poor stream, and recurrent UTIs [1370-1372]. Diagnosis is by VCUG with or without a retrograde urethrogram. In small AUD, endoscopic cutting or deroofing of distal lip of the diverticulum can be sufficient treatment. Larger diverticulum requires excision with subsequent two layered urethroplasty; or marsupialisation with staged urethroplasty. In cases of urosepsis and obstructive uropathy, a suprapubic catheter or temporary urinary diversion (vesicostomy or proximal cutaneous urethrostomy) may be indicated prior to definitive surgical management [1373, 1374]. Anatomically, AUVs have normal corpus spongiosum development whereas AUDs do not [1374].

- **Syringocele**

Cowper's glands are two bulbourethral glands that are located within the urogenital diaphragm which open into the urethra 1-2 cm distal to the sphincter. Syringocele is the cystic dilatation of these glands. The aetiology can be congenital or acquired (trauma or infection). It has been classified as simple, imperforate, perforate and ruptured [1375]. A simpler grouping is suggested as to merge simple, perforate and ruptured ones into "open syringocele" and imperforate to "closed syringocele". Closed syringoceles cause obstructive symptoms and open ones act as a diverticulae and cause post-voiding drippling and sometimes obstruction [1376]. Depending on the syringocele type, patients can present with post-void dribbling, urethral discharge, UTI, perineal pain, haematuria, obstructive voiding symptoms, dysuria or retention. Diagnosis is based on antegrade and/or retrograde urethrogram which shows a cystic defect distal to prostate. If such studies are inconclusive, US and/or MRI may be used. Asymptomatic syringoceles can be managed conservatively. Endoscopic deroofing with various energy sources (cold knife, electrocautery and holmium laser) in both obstructing and non-obstructing syringoceles is an effective method of marsupialisation [1377]. In cases where endoscopic approach is not feasible open correction may be considered.

- **Cobb's collar**

Cobb's collar is a congenital membranous stricture of the bulbar urethra. It is different from congenital obstructive posterior urethral membrane (COPUM), is independent of the veru montanum and external sphincter and is believed to represent a persistence of part of the urogenital membrane [1378]. Voiding cystourethrogram shows narrowing in the proximal bulbar urethra with folds extending proximally, a dilated posterior urethra, prominent bladder neck and other findings of infravesical obstruction. Treatment with endoscopic cold-knife incision showed lower recurrence rates than electrocautery [1379].

- **Urethral atresia/hypoplasia**

Male urethral atresia is congenital, complete obstruction of the urethra caused by a membrane that is usually located at the distal end of the prostatic urethra. The urethra distal to this point is usually hypoplastic, presumably from lack of fetal voiding [1380]. Urethral atresia is associated with bladder distention, VUR, hydronephrosis and renal dysplasia [1381]. Most cases reported have the phenotypic characteristics of the prune belly syndrome. Antenatal intervention may be beneficial in terms of fetal survival [1382]. Although progressive augmentation by dilating the urethra anterior (PADUA) procedure was described as a treatment modality, the majority of cases require some form of supra-vesical diversion [1380, 1381].

- **Posterior Urethral Polyps (PUP)**

Although, PUP does not cause antenatal hydronephrosis, it could cause obstruction later on in life. Posterior Urethral Polyps is a polypoid, pedunculated, fibroepithelial lesion arising in the posterior urethra proximal to the veru montanum. It lies on the floor of the urethra with its tip reaching into the bladder neck and obstruction occurs because of distal displacement of the polyp during micturition [1383]. Patients complain of dysuria, haematuria and obstructive symptoms such as poor urinary stream, intermittent retention episodes. Diagnosis can be suspected by VCUG and/or US but is confirmed during cystourethroscopy. Treatment is usually by endoscopic resection of the polyp. The course of the disease is benign and no recurrences have been reported in the literature [1384, 1385].

3.19.6 *Summary of evidence and recommendations for the management of posterior urethral valves*

Summary of evidence	LE
Posterior urethral valves are one of the few life-threatening congenital anomalies of the urinary tract.	1b
Antenatal therapy could be considered based on ultrasound findings, fetal urine biochemistry, amniotic fluid level, and chromosomal status.	4
Serum creatinine nadir above 0.85 mg/dL is correlated with a poor prognosis.	2a
Neonatal circumcision as an adjunct to antibiotic prophylaxis in PUV patients significantly decreases the risk of developing febrile UTIs during the first two years of life.	1b
Early pharmacological management with oxybutynin may improve bladder function.	1b
Despite optimal treatment, 20% of patients will develop ESRD.	2a
Renal transplantation in these patients is safe and effective, if the bladder function is managed.	3

Recommendations	Strength rating
Drain the bladder in new-borns with a suspected diagnosis of infravesical obstruction and place on antibiotic prophylaxis	Strong
Perform a voiding cystourethrography (VCUG) in patients in whom a diagnosis of posterior urethral valves (PUV) is suspected.	Strong
Attempt endoscopic valve ablation after bladder drainage and stabilisation of the child.	Weak
Consider neonatal circumcision as an adjunct to antibiotic prophylaxis to decrease the risk of urinary tract infection in those with a PUV, especially in the presence of high grade vesicoureteric reflux.	Strong
Offer prolonged urinary diversion (suprapubic/transurethral) for bladder drainage if the child is too small for valve ablation.	Strong
Use serum creatinine nadir as a prognostic marker.	Strong
Assess split renal function by dimercaptosuccinic acid (DMSA) scan or mercaptoacetyltriglycine (MAG3) clearance.	Strong
Consider high urinary diversion if bladder drainage is insufficient to drain the upper urinary tract, or in the absence of clinico-biochemical improvement.	Strong
Monitor and manage bladder and renal function lifelong.	Strong

3.20 Rare Conditions in Childhood

3.20.1 *Urachal remnants*

3.20.1.1 *Introduction*

The urachus is an embryonic structure arising as a result of the separation of the allantois from the ventral cloaca. The allantois appears on day sixteen as a tiny, fingerlike outpouching from the caudal wall of the yolk sac, which is contiguous with the ventral cloaca at one end and the umbilicus at the other. The ventral portion of the cloaca develops into the bladder after cloacal division by the urogenital septum. Thus, the bladder initially extends all the way to the umbilicus [1386]. With progressive foetal development, as the bladder descends into the pelvis, the attachment between the umbilicus and the urachus becomes looser and the apical portion progressively narrows to a small, epithelialised, fibromuscular strand by the fourth or fifth month of gestation. The urachus then obliterates completely by birth, forming the median umbilical ligament [1387-1389].

The urachus varies from 3 to 10 cm in length and from 8 to 10 mm in diameter. It is a three-layered tubular structure, the innermost layer being lined with transitional epithelium, the middle layer composed of connective tissue, and the outermost muscular layer in continuity with the detrusor muscle [1390].

Urachal remnants (URs) originate from failure of the obliteration of the allantois, resulting in a urachal anomaly such as (1) urachal sinus, (2) urachal cyst, (3) vesico-urachal diverticulum, and (4) patent urachus [1387, 1388, 1391]. Most often the urachal anomaly is asymptomatic, but it occasionally may become infected, may cause urinary symptoms, or develop a urachal carcinoma in later life [1390, 1392].

3.20.1.2 Epidemiology

Reports of occurrence rates in the literature vary broadly from a very rare disease in the older literature to a fairly common problem. Robert *et al.* found that URs were present in 61.7% of patients younger than 16 years [1393]. They also noted that the frequency of URs decreased with increasing age. This supports a physiological regression of URs with age. Stopak *et al.* attributed this upsurge to increased awareness among community paediatricians and improvements in US that made visualisation of urachal remnants easier [1394].

Clinical studies and paediatric autopsy studies in the past have shown a much lower incidence. Rubin found an incidence of 1 in 7,610 cases of patent urachus and 1 in 5,000 cases of urachal cysts [1395]. Nix *et al.* noted three anomalies out of 1,168,760 hospital admissions, and Blichert-Toft *et al.* reported five UR cases out of 40,000 patients [1396, 1397]. The incidence rate in males is a little higher than in females [1398, 1399].

The range of the various URs reported in the literature is 10% to 48% for patent urachus, 31% to 43% for urachal cyst, 18% to 43% for urachal sinus and 3% to 4% for urachal diverticulum [1400, 1401].

3.20.1.3 Symptoms

A patent urachus causes continuous or intermittent urine leakage from the umbilicus causing umbilical granulation and erythema in infants [1400]. A urachal cyst is usually diagnosed (1) incidentally, or (2) when it becomes infected causing abdominal pain and discharge of pus from the umbilicus or recurrent UTIs when it drains into the bladder.

The most common symptom is umbilical granulation, discharge and erythema in infants and abdominal pain in older children [1400].

Other symptoms of infected urachal anomalies can vary from high fever, abdominal pain, urinary tract infections, LUTS and/or an abdominal mass [1401-1405]. A urachal diverticulum is often asymptomatic and is usually found incidentally during investigations for other problems. An alternating sinus can empty either into the bladder or the umbilicus and this characteristic is responsible for various presentations [1406]. Infection has been reported as the most common complication in urachal anomalies [1407]. Severe infection may develop into peritonitis and sepsis. Cultures from umbilical discharge usually show Staphylococcus, Streptococcus and E. Coli [1408].

Other congenital anomalies:

Ashley found a simultaneous anomaly in 17 of 46 children, of which VUR was the most common anomaly (6 patients) [1409]. Other investigators reported associated anomalies in cases of persistent URs including meatal stenosis, hypospadias, umbilical and inguinal hernias, cryptorchidism, anal atresia, omphalocele, ureteropelvic obstruction and most frequently, VUR [1399, 1410-1412].

3.20.1.4 Diagnosis

In the majority of cases with complaints of a UR, a careful history and physical examination will confirm the suspicion of a UR. In many patients this can be confirmed by US studies [1393]. An MRI or CT scan may be necessary in a minority of children [1404]. Because of the association with other congenital abnormalities, other studies such as a VCUG or cystoscopy may be undertaken as well. In general, the VCUG is only undertaken when the child also presents with UTI or when the US shows signs of upper tract abnormalities. For the diagnosis per se it is not necessary [1413]; however, a VCUG may be useful for defining the type of urachal anomaly and evaluating a population that may be at higher risk for VUR.

3.20.1.5 Treatment

If a UR is symptomatic, the standard approach has been surgical removal. In most cases it should be done as an elective procedure, following appropriate treatment of active inflammation, and infection is possible. Pre-operative IV-dosage of antibiotic like Cefazolin is generally sufficient. A Pfannenstiel, periumbilical or infraumbilical midline incision can all be used for the open surgical approach [1403, 1414]. Even in symptomatic infants a more conservative approach is possible as well, especially in children less than six months old. Observation and treatment with antibiotics if necessary and radiographic monitoring are a safe approach [1400, 1415, 1416]. Dethlefs *et al.* reported a 90% successful outcome [1402], while Naiditch *et al.* reported that 44 of 78 symptomatic patients resolved under observation [1405]. More recently the laparoscopic approach has been advocated, and shown to be safe [1416-1418]. Surgery is not without risk. The rate of complications following surgical removal varies from 0 to 20%: usually wound infections [1394, 1402-1405, 1414]. Considering the probable additional risk of anaesthesia in very young children any surgical procedure needs to be assessed carefully [1419, 1420].

3.20.1.6 Pathology of removed remnants

Removed specimens may show inflammation or a cystic structure [1402]. Patients presenting without symptoms are as likely to have epithelial elements in the UR as those presenting with symptoms [1404].

3.20.1.7 Urachal cancer

Urachal anomalies are thought to be associated with an increased risk of bladder adenocarcinoma in adults, and urachal adenocarcinoma has an estimated incidence of 0.18 per 100,000 individuals yearly [1421]. These cases account for 0.1 to 0.3% of all bladder malignancies and 20 to 39% of bladder adenocarcinomas [1422]. Urachal adenocarcinoma (UrC) is very rare, especially when one considers that up to 62% of children under 16 years of age may have a UR [1393, 1423]. A study by Copp *et al.* found no association between the presence of UR symptoms and the presence or absence of epithelial tissue in pathology specimens, leading them to conclude that UR symptoms have poor predictive value for malignancy potential in these remnants [1399].

Gleason *et al.* found that 5,721 URs would need to be excised to prevent a single case of urachaladenocarcinoma out of the nearly 65,000 patients reviewed [1421]. Assuming that epithelium is required in the development of urachal adenocarcinoma, the extrapolated Number Needed to Treat (NNT) would be more than 8,000, as nearly 30% of urachal anomalies are void of an epithelial component. Less than 5% of urachal cancers have a non-epithelial origin such as sarcoma [1424]. The presenting symptoms in adults are different from those in children: in a study of 130 adult patients, Ashley *et al.* found that 49% presented with haematuria and 27% with pain. In 51% a urachal carcinoma was diagnosed: adenocarcinoma, with 58% high grade cancer. In addition, 20% had metastases at diagnosis, the overall 5-year cancer specific survival rate in the UrC cohort was 49% [1425]. Stasis of urine and crystallisation promotors such as mucus or desquamated epithelium in the UR are most likely the cause for malignant degeneration as well as stone formation in the adult patient. At present no long-term follow-up on untreated UR in children is available and there is no evidence that urachal anomalies in children increase the likelihood of future malignancy [1400, 1426].

3.20.1.8 Conclusion

Urachal remnants appear to be more common than previously reported. During the first 6-12 months of life spontaneous resolution is common. Excision of symptomatic urachal anomalies is an effective and safe means of treatment, with minimal morbidity. However, most patients with simple and asymptomatic lesions do not appear to benefit from excision, as the risk of malignancy later in life is vanishingly remote. Early intervention (< 6 months of age) should be reserved for patients with persistent documented urine draining from the urachus or a documented abscess. Incidental (US) UR management remains a challenge and should be done with patient and family involvement to make the most informed decision. While surgical intervention has minimal risk and morbidity, it is performed unnecessarily in a large proportion of asymptomatic patients due to the unnecessary removal of non-epithelial containing urachal anomalies and the inability to predict which anomalies will undergo malignant transformation [1427].

3.20.1.9 Recommendation for management of urachal remnants

Recommendations	**Strength rating**
Urachal remnants (URs) with no epithelial tissue carry little risk of malignant transformation.	Strong
Asymptomatic and non-specific atretic urachal remnants can safely be managed non-operatively.	Strong
Urachal remnants incidentally identified during diagnostic imaging for non-specific symptoms should also be observed non-operatively since they tend to resolve spontaneously.	Strong
A small UR, especially at birth, may be viewed as physiological.	Strong
Urachal remnants in patients younger than 6 months are likely to resolve with non-operative management.	Strong
Follow-up: is necessary only when symptomatic for 6 to 12 months.	Strong
Surgical excision of URs solely as a preventive measure against later malignancy appears to have minimal support in the literature.	Strong
Only symptomatic URs should be safely removed by open or laparoscopic approach.	Strong
A voiding cystourethogram is only recommended when presenting with febrile UTIs.	

*3.20.2 **Papillary tumours of the bladder in children and adolescents (Papillary urothelial neoplasm of low malignant potential or transitional cell carcinoma)***

3.20.2.1 Incidence

Papillary tumours of the bladder in children and adolescents are extremely rare and are different from papillary tumours in adults. A "grape-like" papillary tumour in young children will be more likely a rhabdomyosarcoma of the bladder, which are not the focus of this guideline. A papillary tumour in older children or adolescents will be more likely be a papillary urothelial neoplasm of low malignant potential (PUNLMP) [1428]. Children with risk factors, such as previous bladder surgery and immunosuppressive medication can also develop a nephrogenic adenoma of the bladder, also presenting as a papillary tumour of the bladder.

3.20.2.2 Differences and similarities of papillary tumours of the bladder in children and adults

Gender

The overall the risk of a papillary tumour in the bladder in paediatric and young adult patients is approximately double in males compared to females [1429].

3.20.2.3 Risk factors

The majority of these patients have no identifiable risk factors.

3.20.2.4 Presentation

The most common symptom at presentation is haematuria; other less common symptoms include abdominal pain, storage LUTS including frequency, dysuria and at times obstructive symptoms [1429].

3.20.2.5 Investigations and treatment

Ultrasound of the genitourinary tract is the first investigation of choice. It is an excellent screening tool and can often accurately diagnose the nature and location of lesion. In children and adolescents, a bladder US of the full bladder is more sensitive compared with adults due to reduced abdominal fat and thinner muscle layer [1430]. In the event of a need to differentiate the renal or bladder origin of the haematuria, a red blood cell morphology will reveal isomorphic blood cells, differentiating a bladder origin. Urine cytology can be performed, however it has very limited value likely due to the low-grade nature of these tumours in children. Cystoscopy should be reserved if a bladder tumour is suspected on imaging for simultaneous diagnosis and treatment, transurethral resection of the tumour. In children, cystoscopy requires general anaesthesia [1431].

3.20.2.6 Histology

All the lesions in the children and adolescent age-group are identified as papillary and over 85% are solitary [1430]. Papillary bladder tumours in patients younger than twenty years of age have low-grade non-invasive disease (WHO classification) [1432]. These findings let pathologists conclude that in children and adolescents, a papillary bladder tumour can be classified as Papillary Urothelial Neoplasm of Low Malignant Potential (PUNLMP). PUNLMP has minimal or no cytological atypia and it differs from low grade transitional cell carcinoma (TCC) which has cytologic atypia, hyperchromatic nuclei and scattered mitosis [1433].

3.20.2.7 Additional treatment

Mitomycin C and Bacillus Calmette-Guérin have both been used in children but there is no evidence of their efficacy due to the rarity of TCC, and especially of high grade TCC [1429]. Hence, as per current evidence, there is no place for instillations in children.

3.20.2.8 Prognosis, recurrence and surveillance

The prognosis of papillary tumours of the bladder in children is overall good. The recurrence rate in children and adolescents varies from 8 to 15% [1428-1430]. Mean time to recurrence can vary from 11 to 29 months depending on the study, with recurrences occurring up to 90 months from diagnosis; though 64% occur in the first year [1429]. In certain cases, recurrences can be fairly aggressive [1430].

Strategies are based on the guidelines and protocols of papillary tumours of the bladder in adults. It is advised to follow-up children and adolescents with a history of a PUNLMP initially with a short interval of three to six months in the first year, and thereafter at least yearly with urinanalysis for haematuria and an US of the full bladder. In the event of sudden gross haematuria, the evaluation must be performed immediately. If the tumour was completely resected at primary surgery, standard follow-up cystoscopy is not necessary and may be reserved for children or adolescents with a high recurrence risk or suspected recurrence on bladder US [1430]. The exact duration of follow-up is unknown but this Panel recommends follow-up for at least five years.

Inflammatory myofibroblastic tumours of the bladder (IMTB) are rare with nearly 200 cases reported in the literature [1434, 1435]. Around 25% occur in children with a median age at diagnosis of 7.5 years and a median

tumour size of 5.5 cm. Boys and girls are equally affected [1436]. Usually these tumours are benign, with only very few reported malignant cases [1437]. Treatment is mostly surgical with transurethral resection, but local resection, or partial cystectomy maybe needed in selected cases [1436, 1438]. Additionally, a conservative approach is reported [1439]. Histological examination is required to exclude other malignant tumours such as a rhabdomyosarcoma. In children, no recurrence has been reported so far. However due to the malignant potential and few recurrences in adults, follow-up the same as for papillary bladder tumours is recommended.

Eosinophilic cystitis

Though well described in adults, this inflammatory condition is rare in the paediatric population with less than 100 cases reported in the literature to date [1440]. Its etiology remains unknown, but is thought to be incited by IgE mediated attraction of eosinophils to bladder wall followed by mast cell degranulation. It has been linked to medications, specifically antibiotics such as penicillin, chemotherapeutic agents e.g. cyclophosphamide and mitomycin, and chronic bladder catheterisation [1441, 1442]. In children, as opposed to adults, males are more frequently afflicted with seven years being the mean age of presentation, however the condition can be seen throughout childhood even in LUTS [1440, 1443].

Irritative bladder symptoms such as dysuria, frequency, urgency and incontinence are the most frequent and can mimic UTI [1444]. Other symptoms include haematuria, suprapubic tenderness and systemic symptoms. Obstructive manifestations due to mass formation in the bladder wall can result in ureteral obstruction leading to hydro-ureteronephrosis, suprapubic mass in infants in addition to voiding dysfunction [1440, 1443, 1445].

Although associated with allergy only about a third of reported cases had a history of other allergic conditions whereas half had significant eosinophilia or eosinophiluria. Diagnosis is often delayed as symptoms of eosinophilic cystitis (EC) mimic other more common conditions such as UTI and LUTS and most patients will ultimately have undergone imaging studies such as ultrasound, VCUG, CT and MRI, which although not specially diagnostic for the condition, may show bladder wall thickening or even mass formation, with rhabdomyosarcoma constituting an important differential diagnosis. A high index of suspicion for the diagnosis should therefore be maintained when dealing with protracted urinary symptoms not responsive to conventional intervention. Definitive diagnosis can only be attained on tissue biopsy obtained by cystoscopy. Histologically, eosinophilic infiltration of lamina propria and muscularis are seen in acute phases with > 25 eosinophils per high power field considered to be significant [1440, 1443, 1445]. Management is not standardised; removal of any possible allergens is the obvious first step and there are reports of self-limiting course of the disease. However, empirical treatment with corticosteroids, antibiotics, anticholinergics, and antihistamines, in addition to cyclosporine A have been utilised and lead to resolution of symptoms in most cases. Partial cystectomy has been performed in circumscribed lesions that do not disappear spontaneously. No standard follow-up recommendations exist however surveillance is justified as recurrence has been reported in about a third of patients [1440, 1443].

Nephrogenic adenoma

Nephrogenic adenomas (NA) in children are rare benign lesions that usually occur in the setting of previous surgery or chronic irritation of urinary tract [1446]. These benign proliferative lesions are most commonly found in the bladder. There is a significant predominance of girls compared to boys (5:1). The exact pathogenesis is unknown. It is proposed to be a metaplastic process of native urothelium in response to chronic injury. Recent evidence suggest that they can be derived from renal tubular cells that shed, migrate, reimplant and proliferate within urothelial mucosa [1447]. Though they are known to occur concurrently with bladder cancer, there are no *de novo* cases of bladder cancer diagnosed after nephrogenic adenoma. Previous history of bladder surgery such as bladder augmentation or presence of chronic inflammation or irritation is important [1448]. Lesions tend to develop at sites prone to chronic catheterisation injury. Other risk factors include trauma, immunosuppression and radiation. They present with haematuria and storage LUTS with a papillary/polypoid mass on cystoscopy. The recurrence rate is as high as 80% over 4 years [1446]. The final diagnosis is established by cystoscopy and histopathological review of biopsy specimen. Treatment is excision either by transurethral resection which often requires reresections, partial cystectomy or open excision. Again no standard follow-up recommendations exist however regular follow-up with cystoscopy has been advocated especially for patients with augmented bladders as recurrence seem particularly high in this subgroup [1448].

3.20.2.9 Summary of evidence and recommendations for papillary tumours of the bladder in children

Summary of evidence	LE
Majority of paediatric patients have no identifiable risk factors for bladder tumours.	3
There is no evidence on intravesical therapy for bladder tumours in children and adolescents.	4
Prognosis of papillary tumours of the bladder in children is good overall.	3
Inflammatory myofibroblastic bladder tumours are usually benign.	3
Paediatric EC cases are in a third of cases associated with a history of allergic conditions and in 50% with significant eosinophilia or eosinophiluria.	4
Paediatric EC patients usually present with irritative and or obstructive urinary symptoms which can mimic UTI or LUTS thereby leading to delayed diagnosis.	4
In paediatric EC definitive diagnosis can only be attained on tissue biopsy obtained by cystoscopy.	4
In EC treatment with corticosteroids, antibiotics, anticholinergics, and antihistamines, in addition to cyclosporine A have been utilised and lead to resolution of symptoms in most cases.	4
No standard follow-up recommendations exist however surveillance is justified as recurrence has been reported in about a third of patients.	4
NA in children are rare benign lesions that usually occur in the setting of previous surgery or chronic irritation of urinary tract and mainly occurring in the bladder.	4
NA usually presents with haematuria and or storage LUTS and with a papillary/polypoid mass on seen on cystoscopy.	4
NA diagnosis is established by cystoscopy and histopathological review of biopsy specimen.	4
NA treatment is excision either by transurethral resection which often requires reresections, partial cystectomy or open excision.	4
NA recurrence rate is high thereby justifying regular follow-up.	4

Recommendations	LE	Strength rating
Ultrasound is the first investigation of choice for the diagnosis of paediatric bladder tumours.	3	Strong
Cystoscopy should be reserved if a bladder tumour is suspected on imaging for	3	Strong
diagnosis and treatment.	4	Weak
After histological confirmation, inflammatory myofibroblastic bladder tumours should be resected locally.	4	Weak
Follow-up should be every 3-6 months in the first year, and thereafter at least	4	Strong
annually with urinanalysis and an ultrasound for at least 5 years.	4	
Have a high index of suspicion of eosinophilic cystitis (EC) in protracted urinary tract symptoms unresponsive to regular treatment.	4	Strong
Remove any possible allergens as the obvious first step in managing EC.	4	Weak
Eosinophilic cystitis can be managed medically with corticosteroids, antibiotics, anticholinergics, and antihistamines, in addition to cyclosporine A.	4	
Manage nephrogenic adenoma (NA) by resection either transuretherally or by open excision.	4	Strong
Regular endoscopic follow-up especially for augmented patients with NA is justified.	4	Weak

*3.20.3 **Penile rare conditions***

Paediatric lesions of the penis are uncommon but an important part of the paediatric urological practice. The most common of these lesions are cystic penile lesions followed by vascular malformations and neurogenic lesions [1449]. Soft tissue tumours of the male external genitalia are uncommon, but have been described in the paediatric age group and can be malignant [1450].

3.20.3.1 Cystic lesions

- **Epidermal inclusion cysts** are the most common genital cystic lesion and can occur anywhere on the body in both men and women; in the penis it occurs most commonly over the penile shaft varying from 0.1 to 1

cm in diameter. Their epithelium is lined and filled with keratin. It is a painless swelling and can present in the age group with a history of circumcision. Treatment by total surgical excision is mainly indicated for cosmetic or symptomatic (e.g. infection) reasons and should be performed without rupturing the cyst to avoid recurrence [1451].

- **Mucoid cyst of the penis** is synonymous with parameatal cyst or genitoperineal cyst of median raphe; they are midline developmental cysts arising from ectopic urethral mucosa filled with mucoid material. They present since birth but are usually detected during adolescence or later. They are usually asymptomatic developing over penile ventral surface around glans and require surgical removal for either cosmetic, functional or symptomatic reasons [1452].

- **Median raphe cysts** arise from incomplete closure of genital fold during embryogenesis; they are commonly diagnosed in the first decade of life but can present later as they tend to be asymptomatic [1453]. They are either unilocular or multilocular fluid containing cysts, with a mean size of 0.8 cm but cysts larger than 2 cm have also been reported [1454]. Cysts are centred in dermis, with no connection to urethra or epidermis. Histopathologically, there are 4 types: urethral (urothelium-like epithelium, account for 55% cases), epidermoid, glandular and mixed. They can be treated conservatively and can resolve spontaneously or persist. Cyst aspiration is associated with high risk of recurrence and surgical excision is the treatment of choice. Though most penile cysts are asymptomatic, they may get infected resulting in pain and tenderness. They can also present with ulceration, rupture and urinary obstruction if they are close to the urethral meatus. This along with cosmetic issues means that most caregivers and patients opt for surgical excision.

- **Smegmal cysts or smegmal pearls** can be a differential for the cysts above; they are a benign collection of smegma in the sub-preputial space in uncircumcised boys with anticipated spontaneous resolution [1455].

- **Dermoid cyst** are congenital, asymptomatic, firm, solitary, subcutaneous cystic lesions occurring commonly in the region of the corona involving the foreskin. Histopathologically they contain sweat and sebaceous glands with elements of hair and squamous epithelium. Pilosebaceous cysts have been described on the glans; they are benign and usually diagnosed after excision.

3.20.3.2 Vascular malformations

A broad classification of penile vascular lesions into haemangiomas and vascular malformations was proposed by Ramos in 1999 [1456]. **Haemangiomas** develop rapidly at birth and involute slowly; they also include **pyogenic granulomas** which are benign outgrowths of cutaneous capillary vessels formed usually from chronic irritation [1449]. The growth cycle of infantile haemangiomas is divided into early and late proliferative stages, followed by a slow involution phase, completing growth by nine months of age [1457]. Propranolol is currently first line treatment for infantile haemangiomas, the exact mechanism of action is unknown but can include inhibition of angiogenesis, vasoconstriction among others. The dose is in the range of 1.5-2.5 mg/kg, which needs to be continued for 12 to 18 months and then tapered through active or passive weaning to reduce risk of rebound growth [1457]. Other factors leading to rebound growth after propranolol treatment include deep haemangiomas, which occur in about 38% patients despite propranolol therapy, requiring local therapy such as topical timolol, pulsed dye laser or intralesional steroids. After twelve months, the median improvement with treatment is reported as 81% (range 70-90%) based on VAS scores of serial patient photographs.

Vascular malformations are congenital lesions of capillary, lymphatic and venous (or slow-flow) or arterial/arteriovenous (fast-flow) origin that enlarge slowly as the patient grows. These include **glomus tumours**, which are primarily congenital arteriovenous shunts that develop from thermo-regulatory glomus bodies (fastflow vascular malformations). Glomus tumours of the penis can arise on the glans penis, corpora of the penis and as periurethral masses, sometimes accompanied by glomus tumours of fingers and feet [1458]. These are usually asymptomatic at presentation or may have symptoms such as priapism, palpitation and perineal pain. Glomus tumours are benign despite exhibiting high grade nuclear polymorphism. Vascular malformations are usually benign and treated either with laser, sclerotherapy or surgical excision. However, glomus tumours specifically need surgical treatment and follow-up due to the risk of recurrence from incomplete excision [1459].

3.20.3.3 Neurogenic lesions

Penile neurofibroma is an extremely rare lesion arising from perineural and Schwann cells, and occurs usually with evidence of systemic neurofibromatosis or von Recklinghausen syndrome [1460]. They are treated successfully with complete excision [1449]. Rare cases of **malignant schwanomas** on the penis presumably secondary to malignant transformation of benign neurofibromas have been reported in boys with a strong family

history of neurofibromatosis. This type of malignant degeneration of neurofibromatosis occurs in reportedly 5-16% children [1460]. Hence, these patients require long-term follow-up due to risk of recurrence, new tumour formation and malignant transformation.

3.20.3.4 Soft tissue tumours of penis

Mesenchymal tumours are rare in the external genitalia and they require excision in order to differentiate between benign and malignant neoplasms. Histopathological characterisation is essential to ensure malignant tumours receive radical treatment with adjuvant therapy or close follow-up [1450].

Presentation is usually of a painless penile mass, that is non-tender and rubbery on examination. Ultrasound maybe useful in characterising the lesion but is not diagnostic; it can exclude urethral invasion if it is close to urethra [1450]. Once an excision biopsy is performed, if aggressive malignant components are found, a further wider resection may be needed.

Fibrosarcoma is a rare non-rhabdomyosarcoma soft tissue tumour that arises from fibrous tissue. The infantile form of **fibrosarcoma** is rare and those occurring on the penis are even rarer in the paediatric age-group. Surgical intervention has a favourable prognosis in the paediatric age group with long-term survival of 90% in sporadic cases [1461]. Myofibroma is a benign congenital lesion that occurs either as a solitary lesion or as a part of myofibromatosis with multiple soft tissue tumours. Excision is necessary for histological diagnosis [1450].

Primary penile **teratomas** are extremely rare subtype of congenital germ cell tumours, and they tend to be asymptomatic and are subdermal on US with no blood flow on Doppler [1462]. They need aggressive treatment with surgical resection due to their unpredictable behavior and unresponsiveness to chemotherapy. Mature teratomas are benign but immature teratoma or even mixed teratomas with immature components can turn malignant and have the potential to metastasise and recur.

3.20.3.5 Penile Lymphedema

Lymphedema in adults is usually secondary to malignancy or infectious disease affecting lymphatic drainage. In the paediatric age group, however, lymphedema is usually primary and generally very rare, affecting 1.2 per 100.000 persons under the age of 20 years [1463]. Of these, only a very small fraction relates to the genital region. Regardless of underlying aetiology, inefficient lymphatic drainage leads to accumulation of subcutaneous lymph which causes tissue swelling and inflammation. This in turn stimulates adipose deposition and fibrosis further exacerbating enlargement. With time the edematous tissue becomes vulnerable to infection, chronic cutaneous changes and disfigurement [1464]. Additionally, when occurring in the genital region urological complications may ensue; such as phimosis, haematuria, bleeding, bladder outlet obstruction, pain, dysuria, lymphorrhea and severe psychological distress due to resultant deformity [1465, 1466].

In the largest cohort of male genital oedema in the paediatric age group, 92% of cases were primary; of these only 25% had a discernable familial or syndromic association such as Noonan syndrome, lymphedemadistichiasis or Milroy disease [1465]. Secondary genital lymphedema in children has been reported after inguinal surgery, and non-caseating granulomatous lymphangitis as seen with metastatic Crohn's disease [1465-1467]. Average age of onset was reported to be 4.5 ± 6.3 years with 61% presenting in infancy, 13% in childhood and the remaining 26% in adolescence. Edema is usually penoscrotal in 72%, isolated scrotal in 24% and very rarely confined exclusively to the penis in 4%. Moreover, concomitant lower limb edema is the rule in two thirds of cases [1465].

There is no general consensus on diagnostic work-up of these patients. History and physical examination (including family history) is usually sufficient. However lymphoscintigraphy can be used as a confirmatory test, more so for limb than genital edema where results can be difficult to interpret [1465]. Ultrasonography is nonspecific, but has been advocated by some to exclude secondary lymphedema by examining the patency of iliac and caval vessels [1468]. Magnetic resonance imaging is useful to exclude other differential diagnoses such as other venous or lymphatic anomalies [1465].

Conservative treatment is the accepted first-line treatment. The mainstay is compression therapy to maintain and prevent further swelling. This can be achieved by compression stockings and undergarments. Additionally, close observation and protection of the skin to prevent excoriations and infection is essential [1465, 1468]. Compression therapy is however, less effective on genital oedema than it is on limb edema, especially in growing children. When conservative management fails, and especially in symptomatic cases, or in patients with functional impairment, surgical debulking may be necessary. This can either take the form of circumcision in cases where the foreskin is affected or excision of affected skin and subcutaneous tissues with restructuring

and contouring for optimal cosmetic outcome. Complete skin excision and grafting may also be required [1465-1468]. Surgical management can be challenging and needs to be restricted to patients with significant symptoms. Complications include recurrences, continuous lymphatic leakage, haematoma, infection and poor cosmetic outcome [1463, 1468, 1469].

Summary of evidence	LE
Cystic penile lesions are the commonest paediatric penile lesions followed by vascular malformations and neurogenic lesions.	3
Neurofibroma patients require long-term followup due to risk of recurrence, new tumour formation and malignant transformation.	3
Mesenchymal tumours are rare and require excision in order to differentiate between benign and malignant neoplasms.	3

Recommendations	LE	Strength rating
Treatment of penile cystic lesions is by total surgical excision, it is mainly indicated for cosmetic or symptomatic (e.g. infection) reasons.	4	Weak
Propranolol is currently first line treatment for infantile hemangiomas.	2b	Strong
Conservative management is the first-line treatment for penile lymphedema.	4	Strong
In symptomatic cases or in patients with functional impairment, surgical intervention may become necessary for penile lymphedema.	4	Weak

3.21 Emergencies in Paediatric Urology

3.21.1 ***Acute Scrotum***

Refer to Chapter 3.6 “Acute Scrotum”

3.21.2 ***Paraphimoasis***

Refer to Chapter 3.1 “Phimosis and other abnormalities of the penile skin”

3.21.3 ***Priapism***

3.21.3.1 Epidemiology, aetiology and pathophysiology

Priapism is a prolonged full or partial erection of the penis unrelated to sexual stimuli lasting ≥ 4 hours. Although the prevalence of priapism in children is not well reported in literature, it is considered a rare disease. The most common cause of priapism in children is sickle cell disease (SCD), which accounts for about 65% of all cases, followed by leukemia (10%), trauma (10%), idiopathic (10%) and drugs (5%) [1470]. In patients with SCD, the mean age of the first episode of priapism has been shown to be 15 years old, with 25% presenting prepubertally [1471].

3.21.3.2 Classification

Priapism in children can be divided in four groups: ischaemic (low-flow) priapism, stuttering priapism, non-ischaemic (high-flow) priapism, and neonatal priapism.

Ischaemic (low-flow, veno-occlusive) priapism is the most common form (95%) in children. It presents as a painful, rigid erection, with decreased or absent intracavernous arterial inflow. This is considered a medical emergency, since a duration of ≥ 4 hours can cause ischaemia within the corpora cavernosa, and eventually irreversible damage, such as smooth muscle necrosis, corporal fibrosis and erectile dysfunction [1472].

Stuttering priapism presents as recurrent, self-limiting prolonged erections, with intervening periods of detumescence. This often precedes an episode of ischaemic (low-flow) priapism [1473].

Non-ischaemic (high-flow, arterial) priapism is a prolonged erection of the penis lasting ≥ 4 hours not associated with ischaemia. The most common cause is penile, perineal or pelvic trauma, which can lead to the development of an arteriolar-sinusoidal or arteriocavernous fistula, and usually has a delayed presentation after trauma (3 hours – 7 days) [1474].

Neonatal priapism is a very rare condition, with only a few case series described in literature. It presents as a prolonged erection of the penis ≥ 4 hours in a new-born. Sickle cell disease is not associated with neonatal

priapism due to the presence of foetal haemoglobin. It is most commonly idiopathic, but polycythaemia is the most common cause among the identifiable causes [1475]. It has a favourable natural history and benign pathophysiology.

3.21.3.3 Diagnostic evaluation

History

A comprehensive history is critical in priapism and can determine the underlying priapism subtype and cause. Key points in the history of a child with priapism are shown in Table 8.

Table 8: Key points in the history for a child with priapism (adapted from Broderick *et al.* [1476])

Duration of erection
Presence and severity of pain
Previous episodes of priapism and methods of treatment
Medications or recreational drug use
Sickle cell disease, haemoglobinopathies, hypercoagulable states, vasculitis
Trauma to the pelvis, perineum or penis

Physical examination

Inspection and palpation of the penis is recommended to assess the degree of tumescence and rigidity and the involvement of the corpora cavernosa, spongiosum and glans. In ischaemic (low-flow) priapism, typically the glans and corpus spongiosum are flaccid. In non-ischaemic (high-flow) priapism, typically the corpora and the glans are tumescent but not fully rigid (Table 9). If perineal compression results in detumescence, this is suggestive of a non-ischaemic (high-flow) priapism.

Penile imaging

Color doppler ultrasonography of the penis and perineum should be performed in all patients. This can support clinical differentiation between ischaemic (low-flow) and non-ischaemic (high-flow) priapism with 100% sensitivity and 73% specificity in adults [1477], where a peak systolic velocity < 50 cm/s and a mean velocity < 6.5cm/s are suspicious for ischaemia [1478].

Laboratory testing

Laboratory testing with complete blood count (white blood cell count with blood cell differential platelet count) and specific tests for SCD or other haemoglobinopathies should be performed. When ischaemic (low-flow) priapism is suspected, penile blood gas analysis should be performed to differentiate between ischaemic (low-flow) and non-ischaemic (high-flow) priapism (Table 10). However, when non-ischaemic (high-flow) priapism is suspected, penile blood gas analysis should not be the diagnostic of first choice, due to the invasive nature and need for anesthesia.

Table 9: Key findings in paediatric priapism (adapted from Donaldson *et al.*, and Broderick *et al.*, [1470, 1476])

	Ischaemic (low-flow) priapism	**Non-ischaemic(high-flow) priapism**
Corpora cavernosa fully rigid	Typically	Seldom
Penile pain	Typically	Seldom
History of stuttering priapism	Typically	Seldom
Haematological abnormalities	Typically	Seldom
Abnormal penile blood gas	Typically	Seldom
Perineal trauma	Seldom	Typically

Table 10: Blood gas analysis (adapted from Broderick *et al.* [1476])

Source	pO_2 (mmHg)	pCO_2 (mmHg)	pH
Normal arterial blood (room air) (similar values are found in non-ischaemic priapism)	> 90	< 40	7.40
Normal mixed venous blood (room air)	40	50	7.35
Ischaemic priapism (first corporal aspirate)	< 30	> 60	< 7.25

3.21.3.4 Disease Management

Differentiation between ischaemic (low-flow) and non-ischaemic (high-flow) priapism is essential, since clinical management differs between the two. Ischaemic (low-flow) priapism is a medical emergency requiring immediate treatment, where non-ischaemic (high-flow) priapism does not. The management of a child with ischaemic (low-flow) priapism is on most parts similar to adults [1479].

Ischaemic (low-flow) priapism

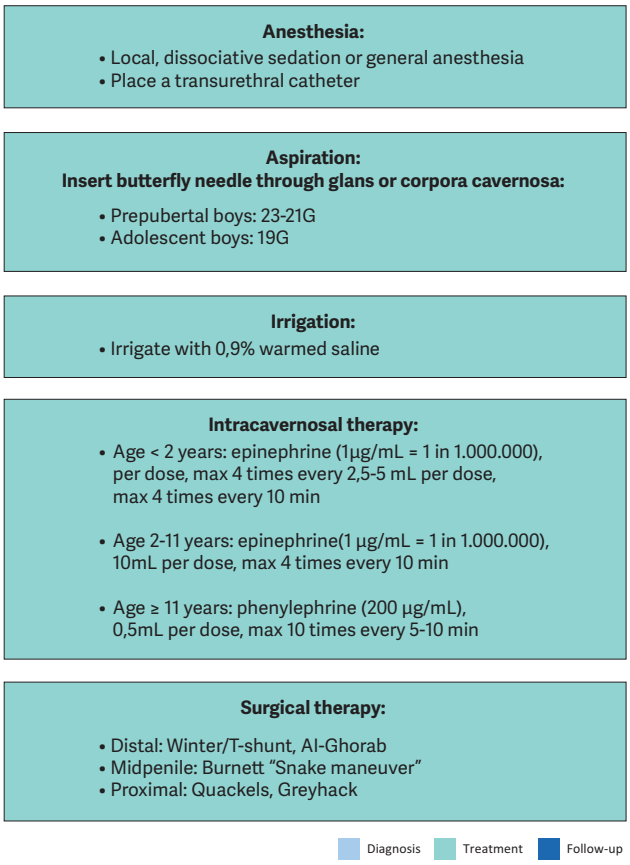
Conservative

Although the amount of evidence is low, conservative treatment should be advised (e.g., physical exercise, urination, cold bath, ejaculation, oral/IV fluids, and analgesia), however if symptoms persist ≥ 2 hours, urgent medical care should be sought [1480].

Medical

If conservative treatment fails, a step-up approach should be used for the management of priapism [1470]. Firstly, anesthesia should be given for the child, either local anesthesia, dissociative sedation or general anesthesia, depending on availability of paediatric anaesthetic expertise and the age and condition of the child. In SCD there are increased risks for general anaesthesia which should be taken into account [1481]. Subsequently a step-up approach should be used for treatment (Figure 14), adapted from Donaldson and adult priapism guideline [1470, 1479].

Figure 14: Step-up approach for the management of Ischaemic (low-flow) priapism in children



Non-ischaemic (high-flow) priapism

This is a very rare entity in the paediatric population. The treatment of non-ischaemic (high-flow) priapism is not emergent. One study demonstrated that conservative management and long-term follow-up yielded no evidence of erectile dysfunction after a median follow-up of 55 months [1482]. Conservative treatment, such as perineal compression or application of ice to the perineum can be successful. If symptoms persist, super-selective angio-embolisation can be performed, however this is technically challenging in children and requires a specialist paediatric vascular radiologist [1483]. Children should be initially treated with a conservative management, reserving embolization for refractory cases [1484].

Stuttering Priapism, and Priapism associated with Sickle Cell Disease (SCD)

The management of a prolonged erection in stuttering priapism is similar to ischaemic (low-flow) priapism. Further management should focus on the prevention of further episodes. Several agents are proposed in literature, such as α-adrenergic agonists, PDE-5 inhibitors, hydroxyurea, β-agonists, or gonadotropin-releasing hormone agonists, but evidence is limited.

The acute management of SCD priapism is closely related to that outlined above. The main caveat is that those with SCD should have their disease medically optimized in close conjunction with paediatric haematology/oncology through a multidisciplinary approach. Hydroxyurea may decrease crisis frequency and severity in SCD-associated priapism [1485]. Unlike urgent surgical management performed in the adult population, a minimally invasive management strategy can be implemented in the paediatric population where an extended period of conservative management that avoids operative management under general anesthetic can be effective in about 60% cases [1486].

Neonatal priapism

Neonatal priapism is usually self-limiting and rarely requires treatment. Careful observation is appropriate in most cases since the majority resolves spontaneously without sequelae. If underlying polycythemia is present, this could be treated by venesection and fluid resuscitation [1487].

3.21.4 Summary of evidence and recommendations for the diagnosis and management of Priapism

Summary of evidence	LE
The most common cause of priapism in children is sickle cell disease.	3
Ischaemic (low-flow, veno-occlusive) priapism is the most common form (95%) in children and is considered a medical emergency.	3
Color doppler ultrasonography of the penis and perineum can support clinical differentiation between ischaemic (low-flow) and non-ischaemic (high-flow) priapism in children.	2b

Recommendations	Strength rating
Perform a doppler ultrasonography in all patients presenting with priapism.	Strong
In children with ischaemic (low-flow) priapism, perform a full blood count and haemoglobinopathy screen to exclude sickle cell disease or other haematological disorders.	Strong
Adopt a multidisciplinary approach when managing patients with SCD-associated priapism.	Strong
Use a step-wise approach starting with the least invasive therapy in patients with ischaemic (low-flow) priapism.	Strong
Manage neonatal and non-ischaemic (high-flow) priapism conservatively in the initial management period.	Strong

Stones

Refer to Chapter 3.16 “Urinary stone disease”

3.22 Paediatric urological trauma

Trauma is the leading cause of morbidity and mortality in children [1482]. This is generally caused by either blunt injuries from falls, car accidents, sports injuries, physical assault, sexual abuse, or penetrating injuries, usually due to falls onto sharp objects or from gunshot or knife wounds.

*3.22.1 **Paediatric renal trauma***

3.22.1.1 Epidemiology, aetiology and pathophysiology

Of all renal injuries, about 25% occur in children, of which 79% is low-grade (I, II or III) and 21% is high-grade (IV or V) [1483]. The most common cause is blunt abdominal trauma (90%), and in blunt abdominal trauma the kidney is the most commonly affected organ, accounting for about 10% of all blunt abdominal injuries [1484]. Children are more likely than adults to sustain renal injuries after blunt trauma due to several anatomical factors, including decreased perirenal fat, weaker abdominal musculature, a relative large size of the kidney in relation to the rest of the body, foetal lobulations which result in a higher likelihood of a local parenchymal disruption, and a less ossified rib cage [1488]. Blunt renal trauma is frequently associated with injury to other organs as well [1489].

3.22.1.2 Classification systems

Renal injuries are classified according to the kidney injury scale of the American Association for the Surgery of Trauma (Table 11) [1490].

Table 11: Renal injury classified according to the kidney injury scale of the American Association for the Surgery of Trauma [1490]

Grade	Type of injury	Description
I	Haematoma and/or contusion	Subcapsular hematoma and/or parenchymal contusion without laceration.
II	Haematoma	Perirenal hematoma confined to Gerota fascia.
	Laceration	Renal parenchymal laceration ≤ 1 cm depth without urinary extravasation.
III	Laceration	Renal parenchymal laceration > 1 cm depth without collecting system rupture or urinary extravasation.
	Vascular	Any injury in the presence of a kidney vascular injury or active bleeding contained within Gerota fascia.
IV	Laceration	• Parenchymal laceration extending into urinary collecting system with urinary extravasation; • Renal pelvis laceration and/or complete ureteropelvic disruption.
	Vascular	• Segmental renal vein or artery injury • Active bleeding beyond Gerota fascia into the retroperitoneum or peritoneum; • Segmental or complete kidney infarction(s) due to vessel thrombosis without active bleeding.
V	Laceration	Shattered kidney with loss of identifiable parenchymal renal anatomy.
	Vascular	• Main renal artery or vein laceration or avulsion of hilum • Devascularized kidney with active bleeding
Vascular injury is defined as a pseudoaneurysm or arteriovenous fistula and appears as a focal collection of vascular contrast that decreases in attenuation with delayed imaging. Active bleeding from a vascular injury presents as vascular contrast, focal or diffuse, that increases in size or attenuation in delayed phase. Vascular thrombosis can lead to organ infarction. Grade based on highest grade assessment made on imaging, at operation or on pathologic specimen. More than one grade of kidney injury may be present and should be classified by the higher grade of injury. Advance one grade for bilateral injuries up to Grade III.		

3.22.1.3 Diagnostic evaluation

In a child who has sustained blunt abdominal trauma, renal involvement can often be suspected from the history, physical examination and laboratory evaluation. Renal involvement may be associated with abdominal or flank tenderness, lower rib fractures, fractures of vertebral pedicles, trunk contusions and abrasions, and haematuria. Vital signs should be monitored during the initial evaluation and give the most reliable indication of the urgency of the situation. 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 [1485]. It is 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. In severe renal injuries, 65% of patients suffer gross haematuria and 33% non-visible haematuria, while 2% have no haematuria at all [1486]. There have been several reports of significant renal injuries that manifest with little or even no blood in the urine [1487].

3.22.1.3.1 Choice of imaging method

FAST-ultrasound

In severe trauma or haemodynamically instable patients, FAST (Focussed Assessment Sonography in Trauma) can be used to identify a hemoperitoneum, with a high specificity (95%) but low sensitivity (33-89%) and negative predictive value (50%). However, sensitivity and specificity for kidney trauma and retroperitoneal hemorrhage is low, therefore it is not recommended as a sole diagnostic tool [1491].

Computed tomography

Computed tomography scanning is the imaging modality of choice in patients with suspicion of renal injuries, since it is widely available, quick and provides accurate grading [1492]. Ideally it is performed in three phases: the arterial phase to detect vascular injury or active bleeding, the nephrogenic phase to detect parenchymal lacerations, and the delayed phase to detect injury of the collecting system or ureter. Furthermore, CT scanning can detect associated other intra-abdominal injuries, which are frequently associated with renal trauma, especially in grade III – V [1489]. Scanning protocol should be adapted for pediatric patients according to ALARA (as low as reasonable achievable) principles to reduce the amount of ionizing radiation as much as possible.

Ultrasound

(Contrast-enhanced) ultrasound can be considered as the sole investigation in patients with mild symptoms and no other indications for CT-scanning, where the mechanism of trauma and the condition of the patient do not suggest the presence of injury to other organs or the urinary tract. Although conventional ultrasound is not accurate to grade renal trauma, there could be a role for contrast-enhanced ultrasound (CEUS) to identify parenchymal lesions, however this technique cannot detect injuries to the urinary tract or collecting system since the contrast agent is not excreted by the kidney [1493]. Ultrasound can be performed in follow-up of a renal trauma to reduce the amount of radiation. However, even in high-grade renal trauma, routine repeat imaging may be avoidable in asymptomatic, stable patients [1494].

3.22.1.4 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. In high-grade renal injuries, a conservative approach is effective and recommended for hemodynamically stable children [1495]. However, this approach requires close clinical observation and intermittent re-assessment of the patient's overall condition. Therefore, a good initial trauma CT with delayed images to check for urinary extravasation is recommended, since patients with a urine leak have higher morbidities, including febrile episodes and an increased requirement of operative or image-guided interventions [1496]. However, early drainage does not seem to prevent persistent urinary extravasation or complications [1497]. Therefore, reserve stenting and/or percutaneous drainage only when the patient is symptomatic [1498]. Emergency intervention is indicated only for haemodynamic instability, and if available angio-embolisation for ongoing or delayed bleeding is preferred compared to open surgery. The results of angio-embolisation were evaluated and were successful in 92% of patients with grade III-IV (294/322) and 76% of grade V (63/82) injuries. Furthermore, the success rate was 90% (312/346) in hemodynamically stable patients, but only 63% (42/66) in hemodynamically unstable patients [1499]. Absolute indications for surgery include persistent bleeding into an expanding or unconfined haematoma with haemodynamic instability. Relative indications for surgery are massive urinary extravasation and extensive non-viable renal tissue [1500].

Follow-up

In paediatric patients with renal trauma, routine blood pressure checks to diagnose hypertension is recommended in the long-term follow-up since posttraumatic renal hypertension rate varies between 4.2 – 18%, especially in cases with concomitant vascular injury [1495, 1501]. However, there is a dearth of long-term data on the risk of developing hypertension in children.

3.22.1.5 Recommendations for the diagnosis and management of paediatric renal trauma

Recommendations	Strength rating
Use imaging in all children who have sustained a blunt or penetrating trauma irrespective of the presence of haematuria, especially when the history reveals a deceleration trauma, direct flank trauma or a fall from a height.	Strong
Use contrast enhanced CT-scanning with delayed images for diagnostic and staging purposes.	Strong
Manage most injured kidneys conservatively.	Strong
Perform angio-embolisation or surgical intervention in case of haemodynamic instability or a Grade V renal injury.	Strong

*3.22.2 **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 [1502]. 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.

3.22.2.1 Diagnostic evaluation

As 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 [1502]. Diagnostic accuracy of CT scanning can be improved by performing a delayed CT scan up to ten minutes after injection of the contrast material [1503]. The most sensitive diagnostic test is a retrograde pyelogram.

It is not uncommon for patients to present several days after the injury, when the urinoma produces flank and abdominal pain, nausea and fever. Due to symptoms being often vague, it is important to remain suspicious of a potential undiagnosed urinary injury following significant blunt abdominal trauma in a child.

3.22.2.2 Management

Immediate repair during abdominal exploration is rare. Minimally invasive procedures are the method of choice, especially since many ureteral injuries are diagnosed late after the traumatic event. Percutaneous or nephrostomy tube drainage of urinomas can be successful, as well as internal stenting of ureteral injuries [1504]. 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, auto-transplantation or ureteral replacement with bowel or appendix [1505].

3.22.2.3 Recommendations for the diagnosis and management of paediatric ureteral trauma

Recommendations	Strength rating
Diagnose suspected ureteral injuries by retrograde pyelogram.	Strong
Manage ureteral injuries endoscopically, using internal stenting or drainage of an urinoma, either percutaneously or via a nephrostomy tube.	Weak

*3.22.3 **Paediatric bladder injuries***

The paediatric bladder is less protected than the adult bladder, and is therefore more susceptible to injuries, especially when 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 during 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 [1506].

3.22.3.1 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 [1507].

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 with axial imaging (e.g., CT scan). Optimal imaging results are achieved through 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 [1508].

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 rupture at its weakest point, i.e., at the dome. Extraperitoneal lesions occur in the lower half of the bladder and are almost always associated with pelvic fractures. A cystogram should demonstrate extravasation into the perivesical soft tissue in a typical flame pattern and the contrast material is confined to the pelvis.

3.22.3.2 Management

Contusions usually present with varying degrees of haematuria and are treated with catheter drainage alone.

3.22.3.2.1 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 [1509]. Usually, after about seven to ten days, a repeat cystogram is performed to ensure adequate healing.

3.22.3.2.2 Extraperitoneal injuries

Non-operative, supportive management with catheter drainage for seven to ten days 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 [1510].

3.22.3.3 Recommendations for the diagnosis and management of paediatric bladder injuries

Recommendations	Strength rating
Use retrograde cystography to diagnose suspected bladder injuries.	Strong
Ensure that the bladder has been filled to its full capacity and an additional film is taken after drainage.	Strong
Manage extra-peritoneal bladder ruptures conservatively with a transurethral catheter left in place for seven to ten days.	Strong
Perform surgical exploration in cases of intra-peritoneal bladder ruptures.	Strong

3.22.4 ***Paediatric urethral injuries***

Except for the penile part of the urethra, the paediatric urethra is quite well protected. In addition, its shape and elasticity means that 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.

3.22.4.1 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 include blood at the meatus, visible haematuria, 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 (although small), 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 and there is a suspected urethral trauma, the catheter should not be removed. Instead, a small infant catheter can be placed into the distal urethra along the catheter to allow the injection of contrast material for a diagnostic scan [1511].

3.22.4.2 Disease management

As these patients may be unstable due to the nature of their injuries, the urologist's initial responsibility is to provide a method of draining and monitoring urine output.

A transurethral catheter should only be inserted if there is a history of voiding after the traumatic event, and if a rectal and pelvic examination, as described above, has not suggested a urethral rupture. If the catheter does not pass easily, an immediate retrograde urethrogram should be performed. A suprapubic tube may be placed in the emergency department percutaneously, or even in the operating room if the patient has to undergo immediate exploration because of other life-threatening injuries.

There are often no associated injuries with a bulbar 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 [1512].

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 erectile dysfunction.

Anterior urethral injury

The data for anterior urethral injury repair is much the same as for adults. Small lacerations can be repaired by simple closure. Complete ruptures without extensive tissue loss are treated with anastomotic repair [1513]. Penetrating injuries require peri- and post-operative antibiotic treatment [1514].

Immediate urethroplasty is generally performed in blunt injuries. The long term-outcomes (patency rate, potency rate) of adult patients treated with immediate urethroplasty is similar to these initially treated with suprapubic diversion and delayed urethroplasty [1515]. The main advantage of performing immediate urethroplasty is that this strategy significantly reduces the time to spontaneous voiding from two to six months to three weeks on average. Spongiosal contusion and haematoma during immediate urethroplasty will make the operation technically more demanding; therefore, immediate urethroplasty should be performed by a dedicated urethral surgeon [1516].

Posterior urethral injury

Unlike anterior urethral injuries with immediate realignment, in children with posterior urethral injuries, a staged approach with delayed repair may be more appropriate.

In children, there is significantly less experience with delayed repair, with a large paediatric series of delayed repair in 68 boys reporting succesfull voiding and continence rate of 90% [1517]. Another study reported strictures and erectile dysfunction in 67% of boys, although all the boys were continent post-operatively [1310]. A follow-up study on fifteen patients who underwent delayed urethroplasty for blunt urethral trauma during childhood reported high long-term success rates, with a low rate of long-term urinary and sexual dysfunction in adulthood [1518].

Revision surgery

A large study of revision urethroplasty analysing revision urethroplasty following pelvic floor urethral injuries in children and adolescents demonstrated that these injuries appeared to be more common in the developing world, with more complex findings and longer gaps. These patients in support of the above findings were best managed with delayed transperineal repair with self-reported success of up to 85% [1519]. On the other hand, a small prospective study demonstrated good results with immediate primary endoscopic realignment in patients with posterior urethral and bladder neck injuries [1520]. This may serve as an alternative to those with permitting

endoscopic anatomy post-injury. A large study exploring outcomes on different urethroplasty techniques in both boys and girls demonstrated that most paediatric pelvic floor urethral injuries can be addressed through a transperineal approach with reasonable long-term outcomes (>80%), however up to 25% patient require further endoscopic/open procedures during follow-up. In challenging cases salvage procedures utilizing vascular-based flaps as a urethral substitute can yield good results, however the numbers lost to follow-up were significant at 40.6% [1521].

In a study of eighteen boys undergoing urethroplasty for strictures (traumatic/iatrogenic), post-void dribbling and urgency were the main patient-reported outcome measures (PROMs) following surgery, with universally high satisfaction rates. PROMs are an important consideration for urologists performing these procedures on children, as they will likely need continued long-term follow-up [1522]. In those who have previously experienced a failed urethroplasty following pelvic-fracture associated urethral injuries, most cases of recurrent posterior urethral strictures of < 3 cm in length can be operated through a perineal urethroplasty with reasonable success rates. Complex and long-segment (higher than 3 cm) strictures require use of ancillary procedures like trans-pubic urethroplasty, substitution urethroplasty and Mitrofanoff appendicovescostomy with complication rates in adolescents of 33% [1523].

3.22.4.3 Recommendations for the diagnosis and management of paediatric trauma

Recommendations	Strength rating
Assess the urethra by retrograde urethrogram in case of suspected urethral injury.	Strong
Perform a rectal examination to determine the position of the prostate.	Strong
Manage urethral injuries conservatively initially if a transurethral catheter can be placed.	Strong
Manage posterior urethral injuries by either: • primary drainage with a suprapubic catheter alone and delayed repair • primary re-alignment with a transurethral catheter	Weak

3.22.5 ***Urosepsis***

Refer to Chapter 3.10 “Urinary tract infections in children”.

3.23 Peri-operative management

3.23.1 Pre-operative fasting, intra-operative fluid therapy, post-operative feeding, fasting and fluid management

3.23.1.1 Epidemiology, aetiology and pathophysiology

Children have a different total body fluid distribution, renal physiology and electrolyte requirements, as well as weaker cardiovascular compensation mechanisms, compared to adults [1524]. During development, children have a high metabolic rate and lower fat and nutrient stores which means they are more susceptible to metabolic disturbances caused by surgical stress [1525]. The metabolic response to anaesthesia and surgery in infants and children is related to the severity of the operation [1526].

3.23.1.2 Disease management

3.23.1.2.1 Pre-operative fasting

Pre-operative fasting has been advocated for elective surgery to avoid the complications associated with pulmonary aspiration during induction of anaesthesia. New regimens include an one hour limitation for clear liquids [1527, 1528] without increased risk of pulmonary aspiration [1529]. Several studies have shown that fasting times in clinical practice often exceed the guidelines with average fasting times of six to ten hours [1528-1530]. Compared to adults, children have a higher metabolic rate and low glycogen stores and impaired gluconeogenesis, which makes hypoglycaemia an important issue to consider, especially in children < 36 months old [1528]. Therefore, it is important to prevent extended fasting times. Clear-liquid carbohydrate drinks have been proposed to reduce these fasting times [1531]. The presence of Type I diabetes does not necessitate different fasting instructions from those for healthy children [1532]. Depending on the length and the scale of the procedure, special attention to appropriate insulin administration, management of hypo- and hyperglycaemia as well as other metabolic abnormalities, is required [1533].

Table 12 provides the current guidelines for pre-operative fasting for elective surgery [1532].

Table 12: Pre-operative fasting times for elective surgery

Ingested material	Minimum fasting period (hours)
Clear liquids	1
Breast milk	3
Formula milk-based products	4
Light meal	6

3.23.1.2.2 Maintenance therapy and intra-operative fluid therapy

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.

The main goal of intra-operative fluid management is to maintain a normal extracellular fluid volume (EFV). During the intra-operative period fluid deficits may be induced by pre-operative fasting, blood loss or third-space losses.

3.23.1.2.3 Post-operative feeding, fasting and fluid management

It is not obligatory to check serum chemistry after uncomplicated surgery in children with normal pre-operative renal and hepatic function. However, if oral intake has been postponed for > 24 hours (e.g., as in intestinal surgery), there is an increased risk of electrolyte abnormalities, requiring further assessment and subsequent management, particularly with potassium. Post-operative findings, such as decreased bowel movements and ileus, may be signs of hypokalaemia.

Children who undergo interventions to relieve any kind of obstructive diseases deserve particular attention, especially due to the risk of polyuria as a result of post-obstructive diuresis [1534]. 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.

In children who have undergone non-abdominal surgery, studies have suggested that gastric motility returns to normal one hour after emergence from anaesthesia [1535]. Early post-operative intake of fluid in children who have undergone minor or non-abdominal urological surgery is associated with reduced post-operative vomiting and lower opioid use [1536] and is therefore encouraged.

Intraperitoneal surgery and the use of bowel may lead to decreased bowel motility in the postoperative period which can lead to paralytic ileus. Experimental and clinical studies have shown that traditional restriction of oral intake, after abdominal surgery, has no basis on scientific evidence and adverse effect on tissue regeneration and enzymatic function has been reported. Due to those deleterious effects of fasting, early enteral nutrition is preferred to parenteral nutrition [1537]. In new-borns, early intragastric, small-volume breast is well tolerated in the post-operative period and seems to provide a trophic effect on gut mucosa [1537].

Chewing gum is a type of sham feeding that promotes intestinal motility, via cephalic-vagal stimulation. It is usually well tolerated and accepted by older children without any contraindication. Although the evidence is limited, it can potentially enhance bowel recovery in the postoperative period in children [1538].

The ERAS protocol is a patient-centred, multimodal approach to optimize postoperative recovery. This protocol includes pre- and intraoperative element such as minimal pre-operative fasting and careful intra-operative fluid management and focuses on post-operative care. The post-operative ERAS protocol suggests starting clear fluid intake on the evening of surgery and a normal diet the day after surgery and thereby early discontinuation of IV fluids. Further focus is on early mobilization, preventing epidurals and omitting or early removal of external tubes [1539].

The implementation of an ERAS protocol has resulted in a shorter length of hospital stays, faster bowel recovery and reduced the needs of post-operative opioid-free administration [1539, 1540]. The implementation of ERAS protocols does not seem to result in higher complication and readmission rates; instead, some studies have even demonstrated a significant reduction in complication occurrence [1539]. When implementing ERAS in children with neurological abnormalities special attention should be given to bowel management with pre-operative treatment of constipation and early post-operative continuation of routine bowel management.

3.23.1.3 Summary of evidence and recommendations for the management of peri-operative fluid management

Summary of evidence	LE
The current evidence recommends reducing clear fluid fasting to 1 h, reducing breast milk fasting to 3h, reducing formula milk-based products to 4h and allowing a light meal 6h before anaesthesia induction for elective procedures.	1
Following abdominal surgery ERAS protocols can be used to reduce recovery times and complications.	1

Recommendations	Strength rating
Ensure shorter pre-operative fasting periods for elective surgeries (one hour for clear liquids, three hours for breast milk, four hours for formula milk-based products and six hours for a light meal).	Strong
Start early postoperative oral fluid intake in all patients scheduled for minor surgical procedures.	Strong
Use enhanced recovery after surgery protocols for abdominal surgery in children with pre-existing normal bowel function.	Strong

3.23.2 ***Post-operative pain management: general information***

3.23.2.1 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 [1541].

3.23.2.2 Diagnostic evaluation

Assessment of pain is the first step in pain management. Several pain assessment tools have been validated according to the child's age, cultural background, mental status, communication skills and physiological reactions [1542]. Depending on the child's age, the 0-10 Numeric Rating Scale, Faces Revised Pain Scale, Face Legs Activity, Cry and Consolability Scale (FLACCS) or Colour Analog Scale, can be used [1543]. One of the most important topics in paediatric pain management is informing and involving the child and caregivers during this process. Patient-family-controlled- analgesia is the preferred pain management in the hospital and at home if provided with the correct information [1544, 1545].

3.23.2.3 Disease management

3.23.2.3.1 Drugs and route of administration

Pre-emptive analgesia is an important concept that aims to induce the suppression of pain before neural hypersensitisation occurs [1546]. Regional anaesthesia is given intra-operatively which can include a regional nerve block or local wound infiltration and has proven to reduce the need for post-operative analgesia [1547]. The WHO's 'pain ladder' is a useful tool for the pain management strategy [1548]. Paracetamol and non-steroidal anti-inflammatory drugs (NSAIDs) are the first choice. As they become insufficient to prevent pain, weak and strong opioids are added to oral drugs to achieve balanced analgesia. A proposed strategy for postoperative analgesia may be as follows:

1. Intra-operative regional block and/or local wound infiltration.
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).

The use of opioids in children has long held a standard role in the post-operative management of pain. Increased recognition of the adverse effects of opioids and prolonged opioid dependency demand a balanced intra-operative administration of opioids [1549]. Intra-operative adequate dosage of paracetamol and NSAIDs results in a decrease in opioid requirement in children [1550, 1551].

3.23.2.3.2 Circumcision

Circumcision requires anaesthesia and proper pain management [1552]. Potential analgesic interventions during circumcision include the use of a dorsal penile nerve block (DPNB) or ring block, topical anaesthetics (depending on age, weight and body surface), and sucrose preferably in combination [1547, 1553]. Caudal blockade methods have similar efficacy compared to DPNB [1554]. However, caregivers should be informed about the more frequent incidence of post-operative motor weakness and micturition problems [1553, 1554].

3.23.2.3.3 Penile, inguinal, and scrotal surgery

Caudal blocks and peripheral nerve blocks (DPNB and pudendal) are commonly used methods for analgesia in hypospadias surgery. Several agents with different doses, concentrations and administration techniques have been used. All have been shown to have adequate postoperative analgesic properties and no increase in post-operative complications was seen [1547, 1555, 1556]. Severe bladder spasms caused by the presence of the bladder catheter can be managed with antimuscarinic medications.

For inguinoscrotal surgery, various regional anaesthesia methods have been investigated, such as transversus abdominis plane block, quadratus lumborum nerve block, ilioinguinal/iliohypogastric nerve blocks and caudal blocks. All have been shown to have adequate postoperative analgesic properties [1557]. Additional local anaesthetics such as clonidine or dexmedetomidine has been shown to prolong the analgesic effect [1558, 1559].

3.23.2.3.4 Bladder and kidney surgery

Continuous local infusion (pain catheter) reduces the need for post-operative opioids [1560-1562], as well as systemic (intravenous) application of analgesics [1563], has been shown to be effective. Ketorolac (NSAID) is an effective agent that decreases the frequency and severity of bladder spasms, the length of post-operative hospital stay and costs and intraoperative opioid administration [1564]. Open kidney surgery is particularly painful because all three muscle layers are cut during conventional flank incision. A dorsal lumbotomy incision may be a good alternative in small children because of the shorter post-operative hospital stay and earlier return to oral intake and unrestricted daily activity [1565]. Caudal and paravertebral blocks continuous epidural analgesia, as well as rectus sheath and transversus abdominis plane blocks have decreased post-operative morphine requirement after abdominal and renal surgery [1566-1568].

3.23.2.4 Summary of evidence and recommendations for the management of post-operative pain

Summary of evidence	**LE**
Adequate paracetamol and NSAIDs use reduces opioid need postoperatively.	1

Recommendations	**Strength rating**
Prevent/treat pain in children of all ages.	Strong
Evaluate pain using age-compatible assessment tools.	Strong
Use pre-emptive and balanced analgesia in order to decrease opioids requirements.	Strong

3.23.3 ***Antibiotics management: general information***

It is well established that peri-operative antibiotics prevent infections following surgery, but limited data are available for antibiotic management in paediatric genitourinary procedures. Antibiotic prophylaxis carried the risk of developing drug-resistant bacteria and adverse effects such as allergic reactions. Furthermore, in childhood some antibiotics are not recommended and their use is discouraged except for in severe cases.

In 2020 Snyder *et al.*, conducted one of the first systematic reviews on perioperative antibiotic practices in the paediatric urology literature [1569]. They reported that the majority of the articles did not provide accurate information on peri-operative antibiotic practices. Other studies demonstrated wide variations in practice patterns for antibiotic usage among paediatric urologists [356, 1570].

Perioperative prophylactic antibiotics in hypospadias repair have been widely debated in the literature. A meta-analysis demonstrated a high risk of bias and a low level of evidence, in terms of postoperative prophylactic antibiotics preventing complications following hypospadias repair [359]. On the contrary, a consensus exists for no perioperative antibiotics following circumcision [1569].

A prospective, randomized, controlled, non-blinded, non-placebo study was performed on the effectiveness of continuous antibiotic prophylaxis in patients with JJ stents, with a total of 105 patients. They concluded that continuous antibiotic prophylaxis reduced the incidence of febrile UTIs, especially in children with a history of febrile UTI and LUTS [1571].

There is a need for standardization of perioperative antibiotic usage for paediatric urological operations, however, a lack of prospective studies and RCT's are the main barriers for creating evidence-based guidelines on this particular topic.

*3.23.4 **Thromboprophylaxis management: general information***

Thromboprophylaxis in children involves preventive measures aimed at reducing the risk of blood clot formation. Unlike adults, the majority of children do not require thromboprophylaxis after surgery. It is only considered in certain high-risk situations such as underlying medical conditions like malignancies, congenital heart disease etc. Moreover, there are very limited data on the safety and efficacy of anticoagulants in paediatric practice.

3.23.4.1 Epidemiology, aetiology, pathophysiology

The incidence of venous thrombo-embolism (VTE) in children is low, but has increased due to an increased use of central venous catheters (CVL) and an improvement in detection [1572]. Some authors suggest an incidence of five to eight cases of symptomatic VTE per 10.000 hospital admissions (0.05%-0.08%) but the true incidence may be higher as the majority of VTEs are clinically silent in children [1573]. In infants, VTE is most often associated with sepsis, congenital haematological disorders, and malignancies. At adolescence, the physiology of the coagulation system matures and additional risk factors such as smoking, obesity, pregnancy, and oestrogen-containing oral contraceptives become relevant. There is a 2:1 preponderance of females among adolescents who develop VTE.

The risk of VTE after urological surgery has been shown to have an incidence of 0.12%, which increases to 0.2% for prolonged hospitalization [1574, 1575].

Before adolescence, the absolute risk of VTE following major surgery, trauma, or immobilization is low, even in children who have thrombophilia [1576]. Therefore, thromboprophylaxis is not recommended.

The risk of developing VTE should focus on adolescents (> 13 years) particularly those with one or more risk factors such as those mentioned above [1577].

General preventive measures are fundamental to prevent VTE and should include: adequate peri- and post-operative hydration, early mobilization after surgery and removal of CVLs as soon as possible. In post-pubertal girls undergoing any kind of surgery, consideration should be given to withholding the combined contraceptive pill for four weeks prior to planned surgery, particularly if there is a strong family history of thrombosis or a known thrombophilic risk factor [1573].

3.23.4.2 Diagnostic evaluation

Identifying thrombophilic risk factors in the family and patient history is important. Symptoms are similar to adult patients with pain, oedema of the dependent areas and development of collateral vessel circulation. However, children with VTE also have some unique presentations such as purpura fulminans. As with adults, the diagnosis of VTE in the upper venous system, is confirmed using doppler ultrasound and if necessary with venography. However, the optimal diagnostic test for lower limb VTE and pulmonary embolism in children is undefined at the present time but ultrasound is the first approach [1578].

3.23.4.3 Disease management

The aims of antithrombotic therapy in children are similar to those for adults with VTE. Management of childhood VTE is often complex, due to the frequent co-existence of medical and surgical diseases, and the fact that limited data is available on the efficacy and safety of these drugs in paediatric practice. A multidisciplinary management approach should be sought.

Medical device and physiological mechanism for thromboprophylaxis

Physical treatments for thromboprophylaxis are the same used for adult patients: graduated compression stockings (GCS), intermittent pneumatic compression (IPC) devices and venous foot-pumps (VFPs). No paediatric sizes of GCS or IPC are yet available, so they are applicable only to older patients, usually those over 40 kg in weight or older than thirteen years. Intermittent pneumatic compression devices have been used for intra- operative use in children aged thirteen years and over who weigh > 40 kg and who are expected to have prolonged surgery [1573, 1577].

The evidence to use these devices is significantly less than for anticoagulant options and few data are available in children and adolescents [1579]. They should be combined with pharmacological prophylaxis. Early mobilization and good hydration should be encouraged in all age patients.

3.23.4.4 Pharmacological treatment for thromboprophylaxis

The use of anticoagulant agents to prevent VTE is very limited in children. None of the preparations are licensed in the paediatric age group. Low molecular weight heparins (LMWHs) have become the mainstay anticoagulant in the paediatric population, both for prophylaxis and treatment due to the more predictable pharmacokinetics compared with unfractionated heparin. Low molecular weight heparins allow less frequent monitoring, and have a lower incidence of serious side-effects. Compared with adult patients, children require higher doses of

LMWH, which decrease with age due to a decreased thrombin production and a high renal clearance. The most commonly used drugs are enoxaparin and dalteparin and the major bleeding rate for prophylactic use of LMWH is low [1573, 1577, 1580].

Children older than thirteen years with multiple risk factors for thrombosis should be considered for thromboprophylaxis with LMWH especially if immobilization for more than 48 hours is expected [1580].

3.23.4.5 Prevention of CVL-related VTE

The presence of a CVL is the most significant risk factor for VTE in children. CVLs placed in the right internal jugular seem to be associated with a lower risk of VTE. There is also evidence that femoral CVLs are associated with a particularly high risk for thrombosis in children [1573]

Thromboprophylaxis did not prevent CVL-related VTE both in prospective studies and RCTs because the majority of these thrombi were transient and resolved spontaneously without therapy [1581].

3.23.4.6 Summary of evidence and recommendations for the management of thromboprophylaxis management

Summary of evidence	LE
The incidence of perioperative thromboembolic events in the paediatric population is generally very low.	1
Patients > 13 years of age with additional risk factors should be considered for venous thrombo-embolism prophylaxis.	1
Standard anti-thrombotic prophylaxis is not recommended due to a lack of high quality RCTs and accepted guidelines concerning perioperative thromboprophylaxis in children.	4

Recommendations	Strength rating
Use physical methods for venous thrombo-embolism prophylaxis (VTE) risk reduction in older children and adolescents who are at increased risk of VTE.	Strong
Consider low molecular weight heparin VTE prophylaxis in children, particularly adolescents, with additional risk factors.	Strong

3.23.5 ***Premedication management: general information***

The majority of children undergoing anaesthesia and surgery develop anxiety that could lead to adverse reactions. Many factors may influence preoperative anxiety [1582]. Anxiety and distress can be prevented or relieved combining: premedication, distraction techniques and parental or caregivers presence. Non-pharmacological age-appropriate methods such as play therapy, toys, storybooks, videos, tablet, mobile phone, can all be useful. A successful plan must therefore take into account the age and temperament of the child [1583].

The most important goal of premedication is to alleviate patients' anxiety and facilitates a smooth separation of the child from their parents/caregivers. Pre-anaesthetic sedatives in children have to be given in a timely fashion pre-operatively, and include midazolam, clonidine, ketamine and dexmedetomidine are used as premedication but no consensus has been reached on the best choice against pre-operative anxiety. Clinicians should select the appropriate premedication depending on the patient's age, disease and psychological status [1584].
Topical anaesthesia should be used to reduce or eliminate the pain and anxiety of an intravenous access placement when an intravenous induction is required. The most commonly used local anaesthetic creams requires 20 to 60 minutes for maximal effect but they can cause vasoconstriction that could make the vein harder to see and cannulate [1582, 1584].

3.23.5.1 Recommendations for premedication management: general recommendations

Recommendations	Strength rating
Use non-pharmacological age-appropriate premedication methods to decrease anxiety levels in children before surgery.	Weak
Use pharmacological premedication to decrease anxiety levels in children and monitor for potential side effects.	Strong

3.24 Basic principles of laparoscopic surgery in children

*3.24.1 **Epidemiology, aetiology and pathophysiology***

The use of laparoscopy and robot-assisted laparoscopic surgery is rapidly increasing and has gained widespread acceptance for many urological surgeries in children [1585]. Laparoscopy is commonly performed for non-palpable testis, nephrectomy, heminephrectomy, varicocelectomy, pyeloplasty, ureteral reimplantation. This expanding scope related to technological advancements allows surgeons to perform more complex procedures in a minimally invasive fashion even in infants and younger children. Generally, well established benefits of minimally invasive surgery are decreased pain, shorter convalescence and better cosmetics compared to traditional open surgery [907, 1586]. When comparing the transperitoneal and retroperitoneal approach, there was no difference in recovery of bowel function [1587]. Additional advantages of robotic surgery over conventional laparoscopy include ergonomics, 3D vision, better manoeuvrability, decreased tremor and easy learning curve. Limitations to be considered are increased operative time, smaller working space at young age, cost and experience of the surgeon and anaesthesiologist. While the success and complication rates are comparable for nephrectomy and pyeloplasty advantages of laparoscopy and robotic surgery for ureteral reimplantation have not been proven and this can only be recommended for experienced centres.

As worldwide experience increases, there is an accumulating awareness about the physiological consequences related to intra- and retroperitoneal CO_2 insufflation in children. In contrast to traditional open surgery pneumoperitoneum may have physiological responses which require close monitoring during surgery and should be taken seriously.

*3.24.2 **Technical considerations and physiological consequences***

3.24.2.1 Pre-operative evaluation

Laparoscopy in children requires specific anaesthetic precautions. Physiological effects of CO_2 pneumoperitoneum, positioning of the patient and in potentially increased operative time need to be considered by the anaesthesiology team. Therefore, a detailed medical examination and risk assessment is mandatory pre-operatively. Especially the cardiac and pulmonary system should be assessed since increased intra-abdominal pressure may lead to decreased ventricular preload [1588].

3.24.2.2 Abdominal insufflation

Abdominal insufflation is the main principle of laparoscopic surgery to create working space for the surgeon. Carbon dioxide is most commonly used for insufflation in laparoscopic centres throughout the world. Other alternatives reported are nitrous oxide, helium, argon and air. However, CO_2 is considered to be the best available gas as it is colourless, cheap, has high solubility in the vascular system [1589] and is excreted by the pulmonary system making it the safest option. Smaller children and infants absorb more CO_2 than older children [1590], suggesting the need for more attention both during and early after laparoscopic surgery for these children.

Most complications of laparoscopy are attributable to gaining access to the abdominal cavity. One study reporting complications of > 5,400 paediatric laparoscopic surgeries showed that there was an overall complication rate of 5.3% of which 4.2% were related to problematic insufflation (subcutaneous emphysema, gas embolism, injury to the organs and vascular structures, mis-insufflation etc.) [1591]. There are two main and well-established techniques for initial access to the abdomen or retroperitoneum: open technique (Hasson) and Veress needle. Studies comparing these two different access techniques in paediatric laparoscopic urological procedures showed similar complication rates [1592]. The vast majority of the complications were minor and related to lack of surgical experience. Particularly in infants and smaller children, the open access technique is recommended by the Panel to reduce the chance of complications.

Elasticity of the abdominal wall is age-related and is higher in infants and small children compared to older children [1593].

Pneumoperitoneal pressure (PnP in mmHg) is one of the critical points that needs to be carefully considered by laparoscopic surgeons. An RCT compared two different pneumoperitoneal pressure groups (6-8 mmHg vs. 9-10 mmHg) in infants less than 10 kg [1594]. It demonstrated that higher pressures were associated with more pronounced respiratory and haemodynamic changes as well as increased post-operative pain scores and prolonged time to resume feeding.

3.24.2.3 Pulmonary effects

After intra-abdominal insufflation the diaphragm is pushed upwards due to increased abdominal pressure. This leads to decreased total pulmonary compliance. Combined with CO_2 absorption this may lead to hypercarbia and acidosis, particularly in case of prolonged operative time or low pulmonary reserve such as in infants.

Trendelenburg position may also aggravate the situation in operations in the pelvic region, such as anti-reflux or bladder neck surgeries. Several studies revealed increased end tidal CO_2 (ET CO_2) related to CO_2 absorption [1590, 1595, 1596]. One study showed a 33% increase in ET CO_2 in the majority of neonatal laparoscopic and thoracoscopic procedures [1597]. Shorter operative time and lower intra-abdominal pressures decrease the risk of increased ET CO_2. Hypoxemia is rarely seen, even in neonates and can easily be adjusted by increasing minute ventilation. These findings highlight the importance of close monitoring of the children.

3.24.2.4 Cardiovascular effects

Intra-abdominal pressure, CO_2 absorption and positioning may also affect the cardiovascular system. It has been shown in adults that after initiation of pneumoperitoneum, cardiac output and stroke volume decrease while mean arterial pressure, central venous pressure and systemic vascular resistance increase [1598]. Similar outcomes have been reported during paediatric laparoscopy with some nuances. Cardiac output was 30% decreased while blood pressure remained stable during laparoscopic orchidopexy with PnP of 10 mmHg in children between aged 6-30 months [1599]. When PnP was lowered from 12 mmHg to 6 mmHg, cardiac index and other vascular parameters normalised [1600]. Using high intra-abdominal pressures in infants with congenital cardiac abnormalities may result in re-opening of cardiac shunts such as the foramen ovale and ductus arteriosus [1601]. Although cardiovascular effects of using high PnP are clinically measurable, they may not have a significant clinical impact on healthy children. However, it is clear that using lower pressures is safer especially in smaller children.

3.24.2.5 Effects on renal function

A study measuring renal oxygenation with NIRS (Near-infrared spectroscopy) during laparoscopy showed that pneumoperitoneum might have a negative effect on renal oxygenation [1602]. However, this effect was reversible after desufflation. Other studies showed pneumoperitoneum may also have adverse effects on renal blood flow [1603]. High intra-abdominal pressures and reverse Trendelenburg position may cause decreased glomerular filtration rate and decreased urine output. One study has shown that 88% of infants and 14% of children more than one year old develop anuria within 45 minutes after initiation of PnP with 8 mmHg [1604]. However, urine output recovers with temporary polyuria after the operation. Although the clinical relevance of decreased urine output seems insignificant, it is important to monitor the fluid and electrolyte balance of the children during and after laparoscopic surgery.

3.24.2.6 Effects on neurological system

Another effect of pneumoperitoneum is increased intracranial pressure (ICP) which normalises after desufflation of the abdomen [1605]. Trendelenburg position, high PnP and hypoventilation are additional risk factors for increased ICP. Laparoscopy is therefore contraindicated in patients with intracranial space occupying lesions [1606]. Children with ventriculo-peritoneal shunts require precautions with regards to shunt drainage, however laparoscopy is not contraindicated [1607].

3.24.2.7 Comparison of robot-assisted laparoscopic surgery versus laparoscopic surgery

No physiological differences are expected between the two approaches since pneumoperitoneum needs to be achieved in the same manner. However, a systematic review comparing robot-assisted laparoscopic pyeloplasty to conventional laparoscopy in infants and children showed no differences in terms of operative success and redo rates between the two techniques [1608]. As for operative time, hospital length of stay and complication rates, the robotic approach appears to be slightly superior in children [909, 1609]. However, in the infant population, operative time was longer in the robot-assisted approach as compared to conventional laparoscopy and there was a higher complication rate, mainly due to a higher rate of port-site hernias [1610]. The robot-assisted approach might aid in filling the gap to minimally invasive surgery for paediatric urologists as it has a shorter learning curve and does not necessarily require prior laparoscopic experience. Downsides to the robotic approach are the size of the instruments, accessibility and costs [909, 1608].

3.24.3 *Summary of evidence and recommendations for laparoscopy in children*

Summary of evidence	LE
Laparoscopy and robotic-assisted laparoscopic surgery can safely be performed in children	1
The general benefits of laparoscopy are decreased pain, shorter convalescence and better cosmetics compared to traditional open surgery.	1
Limitations to be considered are increased operative time, smaller working space with young age, cost, surgeon and anaesthesiologist experience.	1
Pneumoperitoneum may have physiological effects which require close monitoring during surgery and should be taken seriously.	2

Recommendations	Strength rating
Use lower intra-abdominal pressure (6-8 mmHg) during laparoscopic surgery in infants and smaller children.	Strong
Use open access for laparoscopy in infants and smaller children.	Strong
Monitor for laparoscopy-related cardiac, pulmonary and diuretic responses.	Strong

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5. CONFLICT OF INTEREST

All members of the Paediatric Urology Guidelines Panel have provided disclosure statements on all relationships that they have that might be perceived to be a potential source of a conflict of interest. This information is publically accessible through the European Association of Urology website: http://www.uroweb.org/guidelines/. This Guidelines document was developed with the financial support of the EAU. No external sources of funding and support have been involved. The EAU is a non-profit organisation, and funding is limited to administrative assistance and travel and meeting expenses. No honoraria or other reimbursements have been provided.

6. CITATION INFORMATION

The format in which to cite the EAU Guidelines will vary depending on the style guide of the journal in which the citation appears. Accordingly the number of authors or whether, for instance, to include the publisher, location, or an ISBN number may vary.

The compilation of the complete Guidelines should be referenced as:
EAU Guidelines. Edn. presented at the EAU Annual Congress Paris 2024. ISBN 978-94-92671-23-3.

If a publisher and/or location is required, include:
EAU Guidelines Office, Arnhem, The Netherlands. http://uroweb.org/guidelines/compilations-of-all-guidelines/

References to individual guidelines should be structured in the following way:
Contributors' names. Title of resource. Publication type. ISBN. Publisher and publisher location, year.

EAU Guidelines on Renal Transplantation

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1. INTRODUCTION

1.1 Aim and objectives

The European Association of Urology (EAU) Renal Transplantation Guidelines aim to provide a comprehensive overview of the medical and technical aspects relating to renal transplantation. It must be emphasised that clinical guidelines present the best evidence available to the experts but following guideline recommendations will not necessarily result in the best outcome. Guidelines can never replace clinical expertise when making treatment decisions for individual patients, but rather help to focus decisions - also taking personal values and preferences/individual circumstances of patients into account. Guidelines are not mandates and do not purport to be a legal standard of care.

1.2 Panel Composition

The EAU Renal Transplantation Guidelines panel consists of an international multidisciplinary group of urological surgeons, a nephrologist and a pathologist. All experts involved in the production of this document have submitted potential conflict of interest statements which can be viewed on the EAU website: http://www.uroweb.org/guideline/renal-transplantation/.

1.3 Available publications

A quick reference document, the Pocket Guidelines, is available in print. These are abridged versions which may require consultation together with the full text version. All are available through the EAU website: http://www.uroweb.org/guideline/renal-transplantation/.

1.4 Publication history

The EAU published the first Renal Transplantation Guidelines in 2003 with updates in 2004 and 2009. A comprehensive update of the 2009 document was published in 2017. This document is an update of the 2017 Renal Transplantation Guidelines.

2. METHODS

2.1 Introduction

For the 2024 Renal Transplantation Guidelines, new and relevant evidence was identified, collated and appraised through a structured assessment of the literature. Broad and comprehensive literature searches, covering the Renal Transplantation Guidelines were performed, covering a time frame between May 31st 2020 and 1st April 2023. Databases searched included Medline, EMBASE, and the Cochrane Libraries. Detailed search strategies are available online: http://www.uroweb.org/guideline/renal-transplantation/.

Recommendation within the Guidelines are developed by the panels to prioritise clinically important care decisions. The strength of each recommendation is determined by the balance between desirable and undesirable consequences of alternative management strategies, the quality of the evidence (including certainty of estimates), and the nature and variability of patient values and preferences. This decision process, which can be reviewed in the strength rating forms which accompany each guideline statement, addresses a number of key elements:

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

Strong recommendations typically indicate a high degree of evidence quality and/or a favourable balance of benefit to harm and patient preference. Weak recommendations typically indicate availability of lower quality evidence, and/or equivocal balance between benefit and harm, and uncertainty or variability of patient preference [2].

2.2 Review

This document was subject to independent peer review prior to publication in 2017. Publications ensuing from systematic reviews have all been peer reviewed.

3. THE GUIDELINE

3.1 Organ retrieval and transplantation surgery

*3.1.1 **Living-donor nephrectomy***

The endoscopic (laparoscopic) approach is the preferred technique for living-donor nephrectomy in established kidney transplant programmes [3]. Nevertheless, open surgery, preferably by a mini-incision approach, can still be considered a valid option, despite increased pain in the post-operative period [4].

Endoscopic living-donor nephrectomy (ELDN) includes:

- Pure or hand-assisted transperitoneal laparoscopy;
- Pure or hand-assisted retroperitoneal approach;
- Laparo-Endoscopic Single Site Surgery (LESS);
- Natural Orifice Transluminal Endoscopic Surgery-assisted (NOTES);
- Laparo-Endoscopic Single Site Surgery and robotic-assisted transperitoneal or retroperitoneal approach.

There is strong evidence in support of laparoscopic living-donor nephrectomy (LLDN), including several systematic reviews and meta-analysis, which have compared its safety and efficacy to open donor nephrectomy. Laparoscopic living-donor nephrectomy is associated with similar rates of graft function and rejection, urological complications and patient and graft survival. However, measures related to analgesic requirements, pain, hospital stay, and time to return to work are significantly better for laparoscopic procedures [5-8].

Standard LLDN is usually done through 5 and 12 mm ports, but has also been done with 3 or 3.5 mm ports [9]. According to a recent meta-analysis, hand-assisted LLDN is associated with shorter operative time and warm ischaemia, but equivalent safety and overall results [10]. Laparoscopic living-donor nephrectomy can also be performed with robotic assistance, with equivalent results according to a systematic review [11]. However, the numbers are still low and recent studies, including a meta-analysis, have reported higher complication rates for this approach [12, 13].

Laparo-endoscopic single site surgery nephrectomy allows the surgeon to work through a single incision (usually the umbilicus) with a multi-entry port. The same or a separate incision is then used for kidney withdrawal. Several retrospective and at least three prospective randomised trials demonstrated equivalent safety and results, with a trend towards less pain and better cosmetic results [14, 15]. However, LESS is considered a more technically demanding procedure when compared with classic LLDN and its role is yet to be defined.

Natural orifice transluminal endoscopic surgery-assisted transvaginal nephrectomy avoids the abdominal incision needed for kidney extraction, aimed at minimising scaring and pain. Initial reports suggest that this approach is safe, however experience with this technique is still highly limited [16].

Right LLDN has been considered more difficult, yielding inferior results. However, both left and right LLDN can be performed with equivalent safety and efficacy according to large retrospective studies, systematic reviews and meta-analysis [17, 18].

Laparoscopic living-donor nephrectomy has brought attention to potential failures of different devices such as, endoscopic staplers and locking and non-locking clips, used to secure the renal hilum [17]. There is no scientific evidence that one device is safer than another for securing the renal artery [19-21]. However, the U.S. Food and Drug Administration (FDA) and the manufacturers of locking clips have issued a contraindication against their use in securing the artery during LLDN.

Summary of evidence	**LE**
Laparoscopic living-donor nephrectomy is associated with similar rates of graft function and rejection, urological complications and patient and graft survival to open nephrectomy.	1a
Measures related to analgesic requirements, pain, hospital stay, and time to return to work are significantly better for laparoscopic procedures.	1a

Recommendations	Strength rating
Offer pure or hand-assisted laparoscopic/retroperitoneoscopic surgery as the preferential technique for living-donor nephrectomy.	Strong
Perform open living-donor nephrectomy in centres where endoscopic techniques are not implemented.	Strong
Perform laparo-endoscopic single site surgery, robotic and natural orifice transluminal endoscopic surgery-assisted living-donor nephrectomy in highly-specialised centres only.	Strong

*3.1.2 **Organ preservation***

In kidneys donated after cardiac death (DCD) evidence suggests that warm ischemia contributes to worse graft outcome. Donor hemodynamic parameters (systolic blood pressure, oxygen saturation and shock index: heart rate divided by systolic blood pressure) may be predictors of delayed graft function (DGF) and graft failure; however, further studies are required to validate this [22]. The duration of asystolic warm ischaemia during procurement in DCD donors is associated with increased risk of graft failure. Overall five year graft failure (including primary graft non-function) was associated with longer asystolic warm ischaemia times [23]. Extraction time (beginning with aortic cross-clamp and ending with placement of the kidneys on ice), is an important factor for DGF. Incidents of DGF were 27.8% and 60% at up to 60 minutes and 120 minutes extraction time, respectively [24].

A retrospective study of 64,024 living donor kidney transplants found that CIT, human leukocyte antigen (HLA) mismatch, donor age, panel reactive antibody, recipient diabetes, donor and recipient body mass index (BMI), recipient race and gender, right nephrectomy, open nephrectomy, dialysis status, ABO incompatibility, and previous transplants were independent predictors of DGF in living donor kidney transplants [25]. Five-year graft survival among living donor kidney transplant recipients with DGF was significantly lower than in those without DGF. Delayed graft function increased the risk of graft failure by more than 2-fold [25].

3.1.2.1 Kidney storage solutions and cold storage

There are two main sources for kidney graft injury: ischaemia (warm and cold), and reperfusion injury. The aims of modern kidney storage solutions include: control of cell-swelling during hypothermic ischaemia; maintenance of intra- and extra-cellular electrolyte gradient during ischaemia; buffering of acidosis; provision of energy reserve; and minimisation of oxidative reperfusion injury. There is no agreement on which of the mechanisms is most important for post-ischaemic renal graft function [26]. No storage solution seems to combine all mechanisms. Previously, Euro-Collins was widely used, but is no longer recommended.

Presently, University of Wisconsin (UW), and histidine-tryptophan-ketoglutarate (HTK) solution are equally effective and are standard for multi-organ or single kidney harvesting procedures. The characteristics of HTK are its low viscosity, low potassium concentration and low cost. University of Wisconsin solution has been the standard static cold preservation solution for the procurement of liver, kidney, pancreas, and intestine [27]. University of Wisconsin, HTK, and Celsior solutions have provided similar allograft outcomes in most clinical trials, however, some differences have become apparent in recent studies and registry reports [28, 29]. Marshall's hypertonic citrate solution (MHCS) is also suitable for use in the preservation of human kidneys before transplantation [30]. In experimental studies of kidney preservation, HTK and UW retained a greater capacity to preserve endothelial structure and pH buffering function during warm ischaemia in comparison to MHCS and Celsior, especially in uncontrolled DCD donors [31]. In the absence of a cost-utility analysis, the results of the meta-analysis from the randomised controlled trials (RCTs) comparing UW with Celsior and MHSC in standard cadaver donors, indicate that these cold storage solutions are equivalent [32].

For living donors, in whom immediate kidney transplantation is planned, perfusion with crystalloid solution is sufficient. Kidneys coming from DCD donors, especially those uncontrolled are high-risk marginal organs due to prolonged warm ischaemia periods, and require specific measures in order to diminish the rate of non-function or DGF. More than 60% of kidney grafts currently come from Expanded Criteria Donors (ECD) (any donor aged > 65 years and/or donor aged > 55 years with any of the following: acute renal dysfunction, stroke or arterial hypertension) [33].

Summary of evidence	LE
University of Wisconsin and HTK solution are equally effective and are standard for multi-organ or single kidney harvesting procedures.	1b
A meta-analysis of RCTs indicated that UW and Celsior solution are equivalent in standard cadaver donors.	1a

Recommendations	Strength rating
Use either University of Wisconsin or histidine tryptophane ketoglutarate preservation solutions for cold storage.	Strong
Use Celsior or Marshall's solution for cold storage if University of Wisconsin or histidine tryptophane ketoglutarate solutions are not available.	Strong

3.1.2.2 Duration of organ preservation

Cold ischaemia time should be as short as possible. Kidneys from ECDs after brain death (DBD) and DCD donors are more sensitive to ischaemia than standard criteria donors. Kidneys from DBD donors should ideally be transplanted within a 18 to 21 hour time period; there is no significant influence on graft survival within a 18 hour CIT [32, 34, 35]. Kidneys from DCD donors should ideally be transplanted within 12 hours [36], whilst kidneys from expanded criteria donors should ideally be transplanted within 12 to 15 hours [37, 38].

3.1.2.3 Methods of kidney preservation: static and dynamic preservation

Whichever method is used, cold storage is critical. The use of cold preservation as a therapeutic window to deliver pharmacological or gene therapy treatments could, from an investigational point of view, improve both short- and long-term graft outcomes [39]. Cooling reduces the metabolic rate of biological tissue minimising continuous cellular processes that lead to depletion of ATP and accumulation of metabolic products. Reperfusion with oxygenated blood invokes ischaemia-reperfusion injury. Hypothermic perfusion does not enable normal cellular metabolic function or prevent depletion of energy stores [40]; however, it prevents the deleterious effects of simple cooling, especially in the setting of prolonged warm-ischaemic time in uncontrolled DCD donors. Two meta-analyses suggest that hypothermic machine perfusion reduces DGF compared with static cold storage [41, 42]. Outcomes for primary non-function (PNF) are less clear, but one meta-analysis limited to high quality studies suggests a reduction in PNF rates with hypothermic machine perfusion [42]. A Cochrane systematic review and meta-analysis showed that hypothermic machine perfusion (HMP) reduced the risk of DGF when compared to static cold storage (CS) for kidneys from both DCD and DBD donors [43].

The increased demand for organs has led to the increased use of "higher risk" kidney grafts. Kidneys from DCD donors or grafts coming from ECDs are more susceptible to preservation injury and have a higher risk of unfavourable outcomes [44, 45].

Dynamic, instead of static, preservation could allow for organ optimisation, offering a platform for viability assessment, active organ repair and resuscitation. *Ex situ* machine perfusion and *in situ* regional perfusion in the donor are emerging as potential tools to preserve vulnerable grafts. Preclinical findings have driven clinical organ preservation research that investigates dynamic preservation, in various modes (continuous, pre-implantation) and temperatures (hypo-, sub-, or normothermic) [40].

There are several methods of kidney preservation including:

- Initial flushing with cold preservation solution followed by ice storage. However, the limitations of static CS in preserving marginal organs such as ECD kidneys has led to the increased use of dynamic methods.
- Current dynamic preservation strategies entering clinical practice and the different modalities of their use are: hypothermic machine perfusion, hypothermic regional perfusion, normothermic machine perfusion, normothermic regional perfusion, sub-normothermic machine perfusion and sub-normothermic regional perfusion [40].
- Continuous pulsatile HMP seems to be a good preservation method for marginal organs, either initially or after a period of simple CS (shipping of suboptimal kidneys) [46].
- Some evidence shows that hypothermic dynamic preservation should be controlled by pressure and not flow, using low pressures to avoid pressure-related injury. The perfusion solutions used are specific, and are qualitatively different to CS solution [29].
- Nonoxygenated HMP of the kidney at low perfusion pressures (20-30 mmHg) has been shown to reduce DGF [41]. The largest RCT comparing simple CS with HMP of deceased donor kidneys showed an overall reduced risk of DGF and a survival benefit, most pronounced in ECD kidneys [47]. Hypothermic machine perfusion of kidneys from type III DCD donors decreased DGF with no impact on graft survival [44].
- Hypothermic machine-perfusion reduces the risk of DGF in standard criteria DBD donor kidneys regardless of cold ischaemia time [48].
- Increased vascular resistance and high perfusate injury marker concentrations are risk factors for DGF; however, they do not justify discarding the kidney. The flow perfusion value seems to be an indicator of graft viability in uncontrolled DCD donors, particularly donors with a high creatinine level [49]. However, research is required to identify a strong and reliable measure for predicting kidney viability from machine

perfusion [32]. Perfusion parameters (renal flow and renal vascular resistance) have low predictive values and should not be used as the sole criterion to assess viability of kidney grafts [50].

- The effect of oxygenated HMP was investigated in an RCT initiated by the Consortium on Organ Preservation in Europe on type III DCD kidneys and ECD kidneys [40]. Graft loss was significantly lower after oxygenated HMP compared to HMP [51]. No significant differences between the two groups were shown for DGF, PNF and patient death. No difference in eGFR at one year was observed between HMPO vs. HMP; however, sensitivity analysis, accounting for all-cause graft failure, showed a higher eGFR in HMPO [51].
- A short period of normothermic machine perfusion (NMP) immediately prior to implantation has been shown to improve kidney graft function, replenish ATP and reduce injury in experimental models [52, 53].
- A retrospective study of normothermic regional perfusion (NRP) in uncontrolled DCD donors concluded that NRP appears to decrease graft failure when used a preconditioning technique with subsequent HMP preservation in these donors [54].
- Active research is being developed on preservation of prolonged warm-ischaemically damaged human kidneys (types I and II DCD) by *in situ* normothermic extracorporal hemoperfusion with oxygenation and leukocyte depletion before procurement [55]. Oxygen carriage is achieved by using blood depleted of leukocytes. Potential advantages of this preservation technique are reduction in ischaemia-reperfusion injury as well as the possibility of assessing organ viability.
- Currently there is one registered ongoing RCTs on pre-implantation NMP using an oxygenated, sanguineous normothermic perfusion solution (http://www.isrctn.com /ISRCTN15821205). However, kidney function can be evaluated during NMP by assessing macroscopic appearance of blood perfusion, renal blood flow and urine output [56].
- Continuous subnormothermic machine perfusion and controlled oxygenated rewarming has demonstrated improved creatinine clearance and preservation of structural integrity compared with continuous oxygenated HMP in a research setting [57].

Summary of evidence	**LE**
A meta-analysis of RCTs comparing CS with HMP of deceased donor kidneys showed a reduced risk of DGF for HMP.	1a
Hypothermic dynamic preservation should be controlled by pressure and not flow, using low pressures to avoid pressure-related injury.	2a
Perfusion parameters (renal flow and renal vascular resistance) have low predictive values and should not be used as the sole criterion to assess viability of kidney grafts.	2b

Recommendations	**Strength rating**
Minimise ischaemia times.	Strong
Use hypothermic machine-perfusion (where available) in deceased donor kidneys to reduce delayed graft function.	Strong
Hypothermic machine-perfusion may be used in standard criteria deceased donor kidneys.	Strong
Use low pressure values in hypothermic machine perfusion preservation.	Strong
Hypothermic machine-perfusion must be continuous and controlled by pressure and not flow.	Strong
Do not discard grafts based only on increased vascular resistance and high perfusate injury marker concentrations during hypothermic machine perfusion preservation.	Weak

*3.1.3 **Donor Kidney biopsies***

Donor kidney biopsies can serve different purposes including:

- histological assessment of organ quality prior to transplantation (often referred to as procurement or harvest biopsies);
- histological analysis of focal lesions, especially if there is a suspicion of neoplasia;
- detection of donor derived lesions as reference for subsequent post-transplant biopsies (often referred to as baseline, zero-time or implantation biopsies).

3.1.3.1 Procurement Biopsies

3.1.3.1.1 Background and prognostic value

Procurement biopsies are used for the detection of tissue injury to aid the decision of whether or not a deceased donor kidney is suitable for transplantation. These biopsies are most commonly performed in donors with clinical suspicion of chronic kidney injury (ECDs) [58].

Kidney discard in Europe is rarely based on histology findings [59], as procurement biopsies are not regularly performed for graft allocation in the Eurotransplant region [58]. However, since biopsy findings are the most frequent cause for discarding donor organs in the United States [60-63], their prognostic value has been analysed in numerous studies. A recently published systematic review of studies on donor kidney biopsies revealed a lack of prospective studies and marked heterogeneity regarding the type of lesions being assessed, their scoring, the definitions of post-transplant outcomes and the statistical methods employed [64]. Therefore, the published evidence suggests that the use of procurement biopsies for deciding on suitability for transplantation of donor kidneys may have some important limitations including the following [58, 64, 65]:

- *There is no consistent association between histological lesions observed in donor kidney biopsies and post-transplant outcomes.*

The concept of procurement biopsies in elderly donors was introduced by a study from Gaber *et al.,* in 1995. This study observed significantly worse outcomes in recipients of kidneys with > 20% globally sclerotic glomeruli [66]. However, subsequent studies yielded highly variable results and it cannot be concluded that glomerulosclerosis is independently associated with graft outcomes [64]. A similar variability was also observed for other potentially relevant lesions like arterial injury, interstitial fibrosis and tubular atrophy with each showing predictive value in some studies, but not in others [64].

- *There is no agreement on prognostically relevant lesions and how they should be scored.*

Specific grading systems for donor kidney biopsies have not yet been developed. Lesion scoring in pre-transplant biopsies is mostly based on the Banff consensus for post-transplant renal allograft pathology, which is supported by the 2007 Banff Conference report [67].

Many attempts have been made to use composite semi-quantitative scoring systems to express the global extent of tissue injury in donor kidney biopsies. These scoring systems are mostly based on simple addition of the Banff scores for individual lesions, most commonly glomerulosclerosis, arteriolar hyalinosis, arterial intimal fibrosis, interstitial fibrosis and tubular atrophy and rarely include clinical parameters like donor age [68], serum creatinine values and donor hypertension [69].

A limited number of histological scoring systems are based on modelling analysis [68-72]. Only the Maryland Aggregate Pathology Index (MAPI) [72] scoring system and the Leuven donor risk score [68], use graft failure as their endpoint and have been independently validated in a second cohort. Other studies used surrogate clinical endpoints like DGF [70] and estimated glomerular filtration rate (eGFR) at three months [71] to calculate histological models. In addition, these models were not validated in independent cohorts. The variation in how the components are weighted to achieve the composite score and the different endpoints used may explain the conflicting conclusions in the literature [58, 64, 65].

- *Due to the time constraints of organ allocation procurement biopsies are mostly read on frozen sections by on-call pathologists, which might affect the diagnostic reliability of reported findings.*

This may have substantial impact on the diagnostic reliability of the procedure since frozen sections are prone to morphological artefacts that can impair the detection and scoring of potentially important lesions such as arteriolar hyalinosis and interstitial fibrosis [73, 74]. There is strong evidence that dedicated renal pathologists should examine formalin-fixed paraffin-embedded core-needle biopsies. Paraffin histology employing special stains is technically superior to frozen sections since morphological details are better preserved on paraffin sections than on frozen sections and potentially confounding artefacts can be avoided. Rapid processing of tissue for paraffin histology is technically feasible, but the respective protocols are not universally implemented and are not available on a 24/7 basis in most departments. Another source of variability is the professional experience of the pathologist in charge [75]. Procurement biopsies are commonly read by the on-call general pathologist who frequently has no specific training in renal pathology. A recent study specifically addressing this issue found that the on-call pathologists tended to overestimate chronic injury in biopsies [76].

3.1.3.2 Type and size of biopsy

Many transplant centres obtain wedge biopsies of donor kidneys rather than needle biopsies due to the presumed higher risk of bleeding complications with the latter. Wedge biopsies sample the cortex superficially whereas needle biopsies reach deeper aspects of the cortex. Needle biopsies also allow sampling from different areas of the kidney. Submit 14 or 16 G needle biopsies as obtaining adequate biopsies with 18 G needles requires multiple cores [77]. Several studies comparing wedge with needle biopsies concluded that

needle biopsies perform much better in the evaluation of vascular lesions because interlobular arteries are rarely sampled in wedge biopsies. Both methods were comparable for glomerular or tubulointerstitial lesions [78-81]. It was also demonstrated that glomerulosclerosis is significantly more pronounced in the subcapsular zone compared with deeper areas of the cortex [82]. The problem of insufficient sampling of arteries and over representation of (subcapsular) glomerular scars in wedge biopsies, can only be avoided if particular attention is paid to the correct performance of the biopsy, with a minimal depth of 5 mm [83]. The predictive value of glomerulosclerosis increases significantly with higher numbers of glomeruli in the wedge biopsy, with ideally at least 25 glomeruli required for evaluation [80]. There is limited evidence regarding complication rates in pre-implantation biopsies.

For surgeons who are reluctant to take needle biopsies, the use of a skin punch biopsy device might be an attractive alternative. Skin punch biopsies measure 3 mm in diameter. They have a shorter length than needle biopsies therefore avoiding injury to large calibre arteries at the corticomedullary junction whilst still sampling tissue from deeper areas of the cortex [84].

3.1.3.3 Summary of evidence and recommendations

Summary of evidence	**LE**
Individual histologic lesions like glomerulosclerosis, arterial luminal narrowing or tubulointerstitial injury observed in donor kidney biopsies have limited prognostic value for long-term allograft survival.	3
Composite histological scoring systems provide a more comprehensive measure of overall organ damage. However, published scoring systems still lack independent validation and robust thresholds.	3
Size of the biopsy is of critical importance for its diagnostic value. An adequate biopsy reaches beyond the immediate subcapsular area (≥ 5 mm) and contains ≥ 25 glomeruli and ≥ one artery. Needle biopsies, wedge biopsies or specimens obtained with a skin punch biopsy device will result in equally adequate biopsies if sampling is properly performed. Obtaining adequate biopsies with 18 G needles is difficult and requires multiple cores.	3

Recommendations	**Strength rating**
Do not base decisions on the acceptance of a donor organ on histological findings alone, since this might lead to an unnecessary high rate of discarded grafts. Interpret histology in context with clinical parameters of donor and recipient including perfusion parameters where available.	Strong
Use paraffin histology for histomorphology as it is superior to frozen sections; however, its diagnostic value has to be balanced against a potential delay of transplantation.	Strong
Submit 14 or 16 G needle core biopsies, wedge biopsies or skin punch biopsies for histopathology.	Weak
Procurement biopsies should be read by a renal pathologist or a general pathologist with specific training in kidney pathology.	Strong

3.1.3.4 Implantation biopsies

Implantation biopsies are used to provide baseline information on donor kidney injury for comparison with subsequent post-transplant kidney biopsies. Baseline biopsies can be essential for clear distinction between pre-existing damage and acquired lesions. They are particularly valuable in cases of thrombotic microangiopathy, arteriolar hyalinosis or acute tubular injury. In contrast to procurement biopsies that are obtained at the time of organ harvesting, implantation biopsies are usually taken before implantation in order to cover potential effects of cold ischaemia time. Their diagnostic contribution has not been formally quantified in the literature which might be due to the difficulties of measuring the value of implantation biopsies for improving diagnoses. Despite the lack of formal studies investigating their value it seems very reasonable to perform implantation biopsies in deceased donor kidneys.

3.1.4 ***Living and deceased donor implantation surgery***

3.1.4.1 Anaesthetic and peri-operative aspects

Good communication between nephrologists, anaesthetists and surgeons is required for optimal anaesthetic and peri-operative care of the renal transplant patient. Anaesthetic care of the living kidney donor [85] and renal transplant recipient [86] have been reviewed and recent guidelines from the European Renal Association-European Dialysis and Transplantation Association (ERA-EDTA) [87] are cross referenced.

3.1.4.2 Immediate pre-op haemodialysis

Routine use of haemodialysis immediately prior to renal transplantation is not indicated [87]. Hyperkalaemia is the most common indication for haemodialysis pre-operatively. The risks of haemodialysis compared with medical therapy must be considered along with the risks of intra-operative fluid overload, electrolyte and acid-base disturbances, particularly where a deceased donor kidney is transplanted with a significant risk of DGF. Pre-operative haemodialysis may initiate a pro-inflammatory state, delay surgery, increase the CIT and increase the risk of DGF [88].

Summary of evidence	**LE**
Pre-operative haemodialysis has the potential to delay transplantation, increase CIT and increase the risk of DGF.	2

Recommendation	**Strength rating**
Use dialysis or conservative measures to manage fluid and electrolyte imbalance prior to transplant surgery taking into consideration the likelihood of immediate graft function.	Weak

3.1.4.3 Operating on patients taking anti-platelet and anti-coagulation agents

Many patients active on the transplant waiting list have vascular disease and/or a pro-thrombotic condition that should be risk-assessed prior to transplantation. Dual anti-platelet therapy is commonly given to patients with coronary artery stents for six to twelve months; peri-operative management plans for these patients should be discussed with a cardiologist so that the risks of withdrawal of the anti-platelet agent can be fully considered. Options for reversal of anti-coagulation and post-operative anti-coagulation should be discussed with a haematologist prior to patient listing.

Some patients will be active on a transplant waiting list whilst continuing to take anti-platelet and/or anti-coagulation agents. The indication for anti-platelet or anti-coagulation agents should be clearly documented for each individual. Potential increased risk of peri-operative bleeding needs to be weighed against potential harm from arterial or venous thrombosis. In accordance with the American College of Chest Physicians and the European Society of Cardiology guidelines [89, 90], the literature suggests that continuing anti-platelet therapy with aspirin, ticlopidine or clopidogrel does not confer a significantly greater risk of peri/post-operative complications [91], however, the number of patients studied was low. If needed, the effect of anti-platelet agents can be reduced with intra-operative platelet infusions.

Summary of evidence	**LE**
A retrospective single-centre case-control study in patients undergoing kidney transplantation concluded that continuing anti-platelet therapy with aspirin, ticlopidine or clopidogrel does not confer a significantly greater risk of peri/post-operative complications.	3

Recommendations	**Strength rating**
Consider continuing anti-platelet therapy in patients on the transplant waiting list.	Weak
Discuss patients who take anti-platelet and anti-coagulation agents prior to transplant surgery with relevant cardiologist/haematologist/nephrologist.	Weak

3.1.4.4 What measures should be taken to prevent venous thrombosis including deep vein thrombosis during and after renal transplant?

Peri-operative administration of short-acting anti-coagulation agents reduces peri-operative risk of venous thrombosis (including in ileo-femoral and renal veins); however, due to associated increased blood loss administration requires knowledge of individual patient risk factors. None of the current major thrombosis prevention guidelines directly address thromboprophylaxis in the renal transplant peri-operative period. A small RCT [92] showed no difference in early post-operative graft loss or thromboembolic complications with or without prophylactic anti-coagulation. Those administered prophylactic anti-coagulation had significantly lower haemoglobin whilst those administered prophylactic unfractionated heparin had prolonged lymph drainage. Based on this study, routine pharmacological prophylaxis is not recommended in low-risk living donor recipients. Mechanical measures to decrease ileo-femoral deep vein thrombosis (DVT) can be used where there is no contraindication due to peripheral vascular disease particularly where there are concerns about bleeding risks with pharmacological prophylaxis.

Summary of evidence	LE
A small RCT (n=75) showed no difference in early post-operative graft loss or thromboembolic complications with or without prophylactic anti-coagulation.	1b

Recommendation	Strength rating
Do not routinely give post-operative prophylactic unfractionated or low-molecular-weight heparin to low-risk living donor transplant recipients.	Weak

3.1.4.5 Is there a role for peri-operative antibiotics in renal transplantation?

Prophylactic peri-operative antibiotics are generally used in renal transplant surgery but the optimal antibiotic regimen is not known and increasing antibiotic resistance may hamper their effectiveness in this setting. A multicentre, prospective RCT showed no difference at one month in surgical site, bacterial, fungal or viral infection between those receiving a single dose broad spectrum antibiotic at induction of anaesthesia compared to those receiving antibiotic 12 hourly for three to five days [93]. A retrospective comparison of peri-operative intravenous cefazolin prophylaxis compared to no antibiotic showed no difference in infectious complications (surgical site, urinary tract, bacteraemia or central catheter-related infection) in the first month after renal transplantation [94].

Summary of evidence	LE
A multicentre, prospective RCT showed that the incidents of surgical site infection and urinary tract infection were similar in those receiving a single dose broad spectrum antibiotic at induction of anaesthesia and those receiving antibiotic 12 hourly for three to five days.	1b

Recommendation	Strength rating
Use single-dose, rather than multi-dose, peri-operative prophylactic antibiotics in routine renal transplant recipients.	Strong

3.1.4.6 Is there a role for specific fluid regimes during renal transplantation and central venous pressure measurement in kidney transplant recipients?

Careful peri- and post-operative fluid balance is essential for optimal renal graft function. There is no evidence determining if crystalloids or colloids are better for intravenous fluid management during renal transplant surgery, however colloids may be immunogenic. If normal saline (0.9%) is used, monitoring for metabolic acidosis is recommended in the peri-operative period. A prospective double-blind RCT compared normal saline to lactated Ringer's solution as intra-operative intravenous fluid therapy. Serum creatinine at day three post-surgery did not differ between the two groups. However, Ringer's lactate caused less hyperkalaemia and metabolic acidosis than normal saline. Balanced solutions may be the optimal and safer option for intraoperative intravenous fluid therapy [95].

Central venous pressure (CVP) measurement helps anaesthetists guide fluid management. A small prospective non-blinded RCT compared two normal (0.9%) saline regimens: constant infusion (10-12 mL/kg-1/h-1 from start of surgery until reperfusion) and central venous pressure-based infusion (target CVP appropriate to stage of operation) [96]. Central venous pressure directed infusion produced a more stable haemodynamic profile, better diuresis and early graft function. Directed hydration may decrease DGF rates and CVP measurement may help optimise early graft function.

Summary of evidence	LE
A small (n=51) prospective RCT found that use of Ringer's lactate solution was associated with less hyperkalaemia and acidosis compared with normal saline in patients undergoing kidney transplantation.	1b
A small (n=40) prospective RCT comparing constant infusion vs. CVP found that CVP produced a more stable haemodynamic profile, better diuresis and early graft function.	1b

Recommendations	Strength rating
Optimise pre-, peri- and post-operative hydration to improve renal graft function.	Strong
Use balanced crystalloid solutions for intra-operative intravenous fluid therapy.	Weak
Use target directed intra-operative hydration to decrease delayed graft function rates and optimise early graft function.	Strong

3.1.4.7 Is there a role for dopaminergic drugs, furosemide or mannitol in renal transplantation?

Low-dose dopamine (LDD) has been used in renal transplantation due to a perceived improvement in urine output and early graft function. Use of LDD in kidney donors is outside of the scope of this section. Conflicting results prevent a consensus statement on routine use of LDD in transplant recipients. A small (n=20) prospective randomised cross-over study in deceased donor renal transplantation suggested significant improvements in urine output and creatinine clearance in the first nine hours post-surgery without adverse events [97]. By contrast, a retrospective comparison of LDD in the first twelve hours post-deceased donor renal transplantation showed no difference in diuresis or kidney function but those administered LDD (n=57) had increased heart rates, longer intensive therapy unit stay and higher six-month mortality than those not treated with LDD (n=48) [98].

Considerable variation exists in the use of diuretics during renal transplant recipient surgery and there is little evidence to suggest any benefit from their use [99]. No evidence on the use of mannitol during renal transplant recipient surgery was found during the panel's literature search. Use of mannitol in kidney donors is outside the scope of this section.

Summary of evidence	LE
A retrospective comparative study of LDD treated vs. non-treated renal transplantation patients concluded that LDD administration did not improve kidney function in the first twelve hours post renal transplantation, but did result in increased heart rates, longer intensive therapy unit stay and higher six-month mortality in those receiving LDD.	2b

Recommendation	Strength rating
Do not routinely use low-dose dopaminergic agents in the early post-operative period.	Weak

3.1.5 ***Surgical approaches for first, second, third and further transplants***

Transplant (bench/back-table) preparation is a crucial step in the transplantation process. The kidney must be inspected whilst on a sterile ice slush, removing peri-nephric fat when possible to permit inspection of the quality of the organ and to exclude exophytic renal tumours. Biopsy of the kidney on the back-table may be performed to help in the multifactorial decision-making process regarding the quality and usage of the kidney for both single and/or dual transplantation. Suspicious parenchymal lesions also require biopsy. Techniques for intra-operative kidney biopsy are discussed in section 3.1.3.

The number, quality and integrity of renal vessels and ureter(s) should be established and lymphatics at the renal hilum ligated. The quality of the intima of the donor renal artery should be evaluated. Branches of the renal artery not going to the kidney or ureter(s) should be tied.

In deceased donor kidney transplantation the quality of the aortic patch should be determined. If severe atheroma of the patch, ostium or distal renal artery is seen then the aortic patch and/or distal renal artery can be removed to provide a better quality donor renal artery for implantation. Back table reconstruction of multiple donor arteries is discussed in section 3.1.5.1. The length of the renal vein should be evaluated. Renal vein branches should be secured/tied.

For a deceased donor right kidney, lengthening the renal vein on the back table may be performed if needed with donor inferior vena cava [100]. Techniques for lengthening a short living donor right renal vein from donor gonadal vein or recipient saphenous vein require pre-operative planning and specific consent (discussed in section 3.1.5.1).

The length, quality and number of the ureter(s) should be established. The peri-pelvic and proximal peri-ureteral tissue in the 'golden triangle' should be preserved.

Recommendation	Strength rating
Assess the utility (including inspection) of the kidney for transplantation before commencement of immunosuppression and induction of anaesthesia for deceased donor kidney transplantation.	Strong

3.1.5.1 Single kidney transplant - living and deceased donors

The standard surgical approach for first or second single kidney transplant (SKT) operations remains open kidney transplant (OKT). Emerging surgical technologies using minimal access surgical approaches have been developed and the different surgical approaches (minimally invasive open, laparoscopic and robot-assisted) were compared in a systematic review [101].

An extra-peritoneal approach to either iliac fossa should be used as the operative approach in most first or second single kidney transplant (SKT) operations. There is no evidence to prefer placement of a left or right kidney into either iliac fossa [102]. Peri-iliac vessel lymphatics should be ligated to try and prevent post-operative lymphocele. Appropriate segments of iliac artery and vein should be mobilised to facilitate appropriate tension free vascular anastomoses and the final positioning of the transplanted kidney. There is evidence supporting the benefits of cooling the kidney surface during implantation [103].

Recommendations	Strength rating
Choose either iliac fossa for placement of a first or second single kidney transplant.	Weak
Ligate peri-iliac vessel lymphatics (lymphostasis) to reduce post-operative lymphocele.	Weak

A variety of techniques have been described to help with the anastomosis of a short renal vein. This is most commonly encountered with a right kidney especially from a living donor. To achieve equivalent outcomes with right kidneys appropriate surgical technical manoeuvres may be needed to optimise right kidney implantation.

A number of studies suggest marginally worse outcomes with use of the right compared to left kidney, two large registry studies demonstrate a slightly higher risk of early graft failure using right compared to left kidneys from living donors [104-106]. Registry study of 2,450 paired kidneys, donated after cardiac death, observed with right kidneys: more early surgical complications; an increased risk in DGF (Odds Ratio [OD] 1.46); and inferior one year graft survival (OD 1.62), but not at subsequent time points [105]. However, surgical techniques used to compensate for a right kidney, anastomosis time and surgeon experience were not recorded. A recent registry study of 87,112 deceased-donor kidney recipient pairs reported a modest increase in DGF (adjusted OD 1.15) and all-cause graft failure (adjusted hazard ratio 1.07), within the first six months, associated with use of the right kidney, but there was no association with recipient mortality [107]. Furthermore, data from cohort studies [101, 103] and one registry study [104] suggest equivalent outcomes with either left or right deceased donor kidneys. Meta-analysis of data from one RCT and fourteen cohort studies suggested equivalent graft outcomes [108]. Overall, these findings do not support declining an organ for kidney transplantation based on laterality of kidney offered.

Techniques to manage a short renal vein can be addressed in the donor and/or recipient. Ligation of internal iliac vein(s) may be necessary to elevate the iliac vein and avoid tension on the renal vein anastomosis [102]. Transposition of the iliac artery and vein may enhance the position for the venous anastomosis [109]. The right renal vein may be lengthened. With deceased donor kidneys this is usually done with donor inferior vena cava (IVC) [110]. In living donors, lengthening of the renal vein may be achieved with donor gonadal vein retrieved at donor nephrectomy [111] or with recipient saphenous vein [112], although both require specific consent and in general the other aforementioned techniques are preferred.

Summary of evidence	LE
Prospective cohort studies demonstrated that: • transposition of the recipient iliac vein is an appropriate technical solution to compensate for the short length of the renal vein in right kidney LDN (n=43); • the living donor right kidney renal vein can be successfully lengthened using donor gonadal vein (n=17) or recipient saphenous vein (n=19).	3

Recommendation	Strength rating
Assess the length of the donor renal vein and if it is short consider one of a variety of surgical techniques to optimise the venous anastomosis.	Weak

A history suggesting previous iliac or femoral vein thrombosis should initiate pre-operative imaging to establish patency of one iliac vein and the IVC. An intra-operative finding of an unexpected iliac vein and/or vena cava thrombosis may lead to abandonment of implantation. With pre-operative planning, native renal (orthotopic) or superior mesenteric vein or gonadal vein collaterals can be used.

The external or common iliac arteries are equally good for arterial anastomosis. The internal iliac artery is more frequently affected by atherosclerosis than the external or common iliac arteries. End-to-side anastomosis of donor renal artery to recipient external and/or common iliac artery is recommended in general over an end-to-end anastomosis to the internal iliac artery. The only RCT comparing these techniques suggests no difference [113]. However, the study was limited by small numbers and a high (8%) overall renal artery thrombosis rate.

The sites of the vascular anastomosis should be chosen carefully according to the length of the renal artery and vein to avoid kinking of the vessels when the kidney is placed into its final location, usually in the iliac fossa. The site of the arterial anastomosis should avoid atheromatous plaques in the iliac artery to decrease the risk of iliac artery dissection. The intima of the donor and recipient arteries should be checked prior to commencing the arterial anastomosis to ensure that there is no intimal rupture/flap. If this is found it must be repaired prior to, or as part of, the arterial anastomosis.

A Carrel patch is usually maintained on a deceased donor renal artery although it can be removed if there is either severe ostial atheroma/stenosis (with good quality proximal renal artery) or if the length of the renal artery is too long for the appropriate implantation site on the iliac artery (which is more common with the right renal artery).

Multiple renal arteries supplying a deceased donor kidney can be maintained on a Carrel patch (of appropriate length) and implanted as a single anastomosis. In living donor transplantation, multiple renal arteries require a variety of strategies to achieve optimum re-perfusion [99]. Two arteries can be implanted separately or to achieve a single anastomosis: a very small second artery (especially if supplying the upper pole) may be sacrificed; the two arteries may be joined together (as a trouser graft); or the smaller artery can be anastomosed onto the side of the main artery (end-to-side anastomoses). A lower polar artery may be re-vascularised via anastomosis to the inferior epigastric artery [114]. In living donor transplantation where three or more donor arteries exist consideration should be given to alternate kidney donors. In circumstances using a living donor kidney with three or more donor arteries, strategies include a combination of the above techniques or, after appropriate consent, use an explanted (recipient's own) internal iliac artery graft [115] or saphenous vein graft [116].

In cases where an iliac artery prosthetic replacement has previously been carried out because of severe symptomatic iliac atheroma, the renal artery should be implanted into the prosthesis. Administration of systemic heparin should be considered prior to clamping of a vascular prosthesis [117].

A variety of sutures and suturing techniques for the vascular anastomosis are described, but in general practice, a 5/0 and 6/0 non-absorbable mono-filament polypropylene suture(s) are used for the renal vein and renal artery anastomosis. Despite this, there is no evidence to recommend one suturing technique over another to prevent, for example, transplant artery stenosis. Use of an expanded polytetrafluroethylene suture compared to standard polypropylene suture may reduce blood loss due to a better needle/thread ratio [118].

In third or further transplants the surgical approach must be planned pre-operatively so that appropriate arterial inflow and venous outflow exists with adequate space to implant the new kidney [119, 120]. Nephrectomy of an old transplant kidney may be required prior to transplantation or at the time of transplantation [119]. Mobilisation of the common or internal iliac artery, internal iliac vein or IVC may be required. An intra-peritoneal approach (via the iliac fossa or midline) may be required [121]. Rarely orthotopic transplantation is needed [119, 122].

Evidence suggests that minimising the anastomosis time and/or rewarming time results in reduced DGF [123]. The effect on long term graft function is uncertain, but may also be impacted by short anastomosis time [124].

Summary of evidence	**LE**
A small RCT (n=38) comparing end-to-end anastomosis to the internal iliac artery vs. end-to-side anastomosis to the external iliac artery found that both techniques showed similar results in the post-operative period and at three-years follow-up.	1b
Cohort studies have demonstrated third or further transplants are a valid therapeutic option with reasonable short- and long-term patient and graft survival.	3

Recommendations	Strength rating
Use the external or common iliac arteries for an end-to-side arterial anastomosis to donor renal artery.	Weak
Use an end-to-end anastomosis to the internal iliac artery as an alternative to external or common iliac arteries.	Weak
Check the intima of the donor and recipient arteries prior to commencing the arterial anastomosis to ensure that there is no intimal rupture/flap. If this is found it must be repaired prior to/as part of the arterial anastomosis.	Strong
Pre-operatively plan the surgical approach in third or further transplants, to ensure that appropriate arterial inflow and venous outflow exists with adequate space to implant the new kidney.	Strong

3.1.5.2 Robot-assisted kidney transplant surgery

Robot-assisted kidney transplant (RAKT) surgery using living donor kidneys have now been evaluated in multi-centre prospective non-randomised studies (using IDEAL consortium principles) [125]. Single centre prospective non-randomised studies are on-going addressing RAKT with use of deceased donor kidneys. Both trans-peritoneal and extra-peritoneal approaches for RAKT are described. Potential advantages of RAKT may exist (decreased post-operative pain, incision length and lymphocele rate). Potential issues with RAKT are the exclusion of recipients with severe atherosclerosis or third (or further) kidney transplants, a higher than expected rate of DGF and a small number of reported early arterial thromboses despite carefully selected cases [126]. The learning curve for RAKT has been reported to be 35 cases for experienced surgeons in a retrospective multicentre series of 187 patients undergoing RAKT [127]. Complication and DGF rates decreased significantly and plateaued after the first 20 cases. The rate of Clavien- Dindo grade III/IV complications was 14% during the first ten RAKTs, but only 3% after this [127]. The rate of arterial graft thrombosis (1.6%) was comparable with that for open kidney transplant (0.5 - 3.5%) [127]. A ten year single-centre retrospective analysis of 239 obese RAKT patients concluded that RAKT can be safely performed in obese patients with minimal risk of developing a surgical site infection [128]. A graft failure rate of 7.1% was reported during follow up mostly due to acute rejection. Patient and graft survival was 95% and 93% at three years, respectively [128]. Evidence is too premature to recommend RAKT outside of appropriately mentored prospective studies.

3.1.5.3 Dual kidney transplants

Dual kidney transplant (DKT) is performed when the quality of a single deceased donor kidney is thought to be insufficient for appropriate long-term graft function and that the outcome with both kidneys would be better. A variety of surgical techniques have been described to implant the pair of donor kidneys [129]. These include unilateral extra-peritoneal (UEP) or intra-peritoneal (UIP) and bilateral extra-peritoneal (BEP) or intra-peritoneal (BIP) that can be via a midline [130] or two lateral incisions.

The aim of a unilateral approach is to leave the contralateral iliac fossa intact for future transplantation in the event of graft loss and to reduce CIT for the second kidney transplant [131]. The unilateral approach may require mobilisation and division of the internal iliac vein to facilitate the two renal veins to iliac vein anastomoses. Modifications of the unilateral technique include single renal artery and vein anastomoses (with bench reconstruction) to further reduce CIT for the second kidney [132-134]. Dual kidney transplant takes longer and has higher blood loss than SKT regardless of the technique used. Data suggest shorter operative time and hospital stay with UEP compared to BEP [135] but other data suggest similar outcomes from all DKT techniques. No RCT exists to recommend one technique for all patients or situations.

En-bloc retrieval is performed when kidneys are retrieved from children weighing < 15 kg.

Depending on the size of the donor kidney and size and weight of the adult recipient(s), *en-bloc* transplantation of the two kidneys may be performed or, if appropriate, the aorta and IVC patch may be divided for SKT [136].

3.1.5.4 Ureteric implantation in normal urinary tract

Ureteric anastomotic techniques described for renal transplant recipients with no underlying urological abnormality include: extra (Lich-Gregoir) or intra (Leadbetter-Politano) vesical uretero-neo-cystotomy and uretero-ureterostomy using native ureter. A meta-analysis [137] of two RCTs and 24 observational studies favoured the extra-vesical Lich-Gregoir technique to an intravesical approach leading to reduced overall complications (specifically urine leak, stricture and post-operative haematuria). Fewer urinary tract infections (UTIs) were observed with the extravesical approach when compared with the intra-vesical technique in one RCT [138]. Pyelo- or uretero-ureterostomy to the ipsilateral native ureter has been described as a primary technique in recipients with non-refluxing native ureters [139]. A meta-analysis suggested ureteric stricture, obstruction, and

stone formation were more common after uretero-ureterostomy whereas vesicoureteral reflux and UTIs were more common after uretero-neo-cystostomy [140].

The donor ureter should be kept as short as possible with peri-ureteric fat preserved to ensure adequate ureteric blood supply. The location on the bladder to position an extra-vesical anastomosis was shown in one small RCT to be advantageous at the posterior bladder rather than anterior position to facilitate future endoscopic manipulation if needed, and reported less hydronephrosis post stent removal [141]. In cases where donor ureter has been damaged at retrieval then pyelo-native-ureterostomy or pyelo-neo-cystotomy can be performed. Mono-filament absorbable sutures should be used for the urinary anastomosis to prevent stone formation around the suture material [142].

Summary of evidence	**LE**
A meta-analysis of two RCTs and 24 observational studies favoured the extra-vesical Lich-Gregoir technique for reduced overall complications.	1a
A multi-centre prospective comparison study found the incidence of overall complications was similar for pyelo- and uretero-ureteral anastomosis and that for both procedures no graft was lost due to urological complications.	2b

Recommendations	**Strength rating**
Perform Lich-Gregoir-like extra-vesical ureteric anastomosis technique to minimise urinary tract complications in renal transplant recipients with normal urological anatomy.	Strong
Pyelo/uretero-ureteral anastomosis is an alternative especially for a very short or poorly vascularised transplant ureter.	Strong

Transplant ureteric anastomosis can be performed with or without a ureteric stent. If a stent is placed a second procedure is generally required for removal. A Cochrane review [143] concluded that stents are recommended to reduce major urological complications, especially urinary leak. The optimal timing for stent removal has yet to be defined [144]. A meta-analysis of five RCTS including 568 kidney transplantation patients showed a significant reduction in UTIs for early (≤ 7 days) vs. late removal (≥ 14 days) [145]. No significant differences where observed between the two groups in relation to post-operative complications such as ureteral stricture, ureteral obstruction, and ureteral leakage [145]. A second meta-analysis including 3,612 patients also reported a significant reduction in UTIs with early stent removal (< 3weeks) vs. late removal (> 3 weeks) [146]. No significant differences where observed between the two groups regarding the incidents of ureteral stenosis and ureteral leakage [146].

Most commonly, stents are removed with local anaesthetic flexible cystoscopy unless there is a need to combine with another procedure warranting general anaesthetic. Various techniques to reduce the morbidity of a second procedure involve tying the stent to the catheter or use of percutaneous stents [147].

Recommendation	**Strength rating**
Use transplant ureteric stents prophylactically to prevent major urinary complications.	Strong

Duplex ureters are not infrequently identified at organ retrieval/kidney benching or during work-up for LDN [148, 149]. Duplex ureters can be anastomosed together and then joined to the bladder as one unit (double pant) or kept as two separate anastomoses. This also applies to the two single ureters in DKT in adults or with *en-bloc* transplantation from paediatric donors. The arguments for two separate ureteric anastomoses to the bladder are that an already tenuous blood supply may be further compromised with added suturing and handling, and if there is an issue with one ureter the other should remain unaffected. The advantages to forming one single (two ureter) anastomosis to the bladder are that only one cystotomy is needed; it may be faster and complications may be reduced. There is a lack of high quality evidence relating to duplex ureters.

Recommendation	**Strength rating**
Use the same surgical principals for single ureters to manage duplex ureters and anastomose them either separately or combined.	Strong

3.1.5.5 Transplantation/ureteric implantation in abnormal urogenital tract

The following points should be considered when performing kidney transplantation in the abnormal urogenital tract:

- In patients with an ileal conduit, a kidney transplant may be placed upside down to align the ureter to the conduit and avoid a redundant ureter [150].
- The technique used to implant transplant ureter(s) into an ileal conduit is the same as the method used with native ureter(s) (Bricker; Wallace).
- In bladder augmentation or continent pouches, ureters should be implanted with a tunnel technique or extra-vesically (Lich-Gregoir). The latter is favoured in most patients.
- In patients with a Mitrofanoff catheterisable stoma or continent ileo-caecal pouch with catheterisable stoma, consideration should be given to the positioning of the catheterisable stoma (umbilical or iliac fossa - usually right-side) with clear communication with the transplant surgeons so that the position of any future transplant kidney is not compromised. If an intra-peritoneal placement of a future kidney transplant is likely, then placement of a Mitrofanoff exiting in the iliac fossa is preferable at the umbilicus. If a future kidney transplant is likely in the right iliac fossa then placement of a Mitrofanoff exiting at the umbilicus or left iliac fossa may be preferable.

*3.1.6 **Donor complications***

Living-donor nephrectomy, like any other intervention, is potentially associated with complications and mortality. However, the fact that the operation is performed on a healthy individual amplifies the relevance of any complications. Potential complications should be included in the process of informed consent.

Reported surgical mortality is 0.01% to 0.03% with no apparent alteration due to changes in surgical techniques or donor selection in recent years [151, 152]. According to a recent systematic review (190 studies) and meta-analysis (41 studies) on complications in minimally invasive LDN, reporting on a total of 32,308 LDNs, intra-operative complications occur in 2.2% (the most common being bleeding in 1.5% and injury to other organs in 0.8%) and post-operative complications occur in 7% (infectious complications in 2.6% and bleeding in 1%) [151]. Conversion to open surgery was reported in 1.1%, half due to bleeding and half due to injury to other organs. Surgical re-interventions occurred in 0.6%; the majority due to bleeding or to evacuate a haematoma [151]. A low trigger for conversion or re-operation should be observed in order to minimise the risk of serious complications.

A recent review looked for complications in 14,964 LDNs performed in the U.S. from 2008-2012 and found an overall peri-operative complication rate of 16.8%, gastrointestinal (4.4%), bleeding (3.0%), respiratory (2.5%), surgical/anaesthesia-related injuries (2.4%), and “other” complications (6.6%). Among the sample, 2.4% required intensive care and in-hospital mortality was 0.007% [12].

Major Clavien Classification of Surgical Complications grade IV or higher affected 2.5% of donors. Risk factors for Clavien grade IV or higher events included obesity (adjusted odds ratio [aOR] 1.55, $p = 0.0005$), pre-donation haematologic (aOR 2.78, $p = 0.0002$), psychiatric conditions (aOR 1.45, $p = 0.04$) and robotic nephrectomy (aOR 2.07, $p = 0.002$). An annual centre volume > 50 (aOR 0.55, $p < 0.0001$) was associated with lower risk [12].

3.1.6.1 Long-term complications

Long-term complications are mostly related to the single-kidney condition. Renal function in living donors decreases after donation before improving for many years; however, in the long run it shows signs of slight deterioration [153-155]. There is a steady increase in the incidence of proteinuria; hypertension post-transplant having been shown as the main cause of increased albumin excretion [156]. A meta-analysis found that obesity (BMI > 30) is associated with a significantly lower eGFR and higher blood pressure and proteinuria one year after donation [157]. A study looking at the Norwegian Living Kidney Donor Registry found an increased long-term risk of ischaemic heart disease in live kidney donors when compared with a healthy control group eligible to be donors [158].

The overall incidence of end-stage renal disease (ESRD) (0.4-1.1%) does not differ from the general population [153, 154, 159, 160]. According to a large retrospective study, the majority of ESRD developing after living kidney donation is due to new-onset disease that would have affected both kidneys [161]. However, there are some identified risk factors for deterioration of renal function after donation. According to a study that evaluated 119,769 live kidney donors in the United States, obese (BMI > 30) living kidney donors have a 1.9-fold higher risk for ESRD compared to their non-obese counterparts [162]. Long-term risk of death is no higher than for an age- and co-morbidity-matched population [152, 159].

Health related quality of life (HRQoL), including mental condition, remains on average better than the general population after donation [159, 160, 163]. However, some donors experience significant deterioration in their perceived QoL [163]. While global HRQoL is comparable or superior to population normative data, some factors identifiable around time of donation including longer recovery, financial stressors, younger age, higher BMI, lower education, smoking and higher expectations prior to donation, may identify donors more likely to develop poor HRQoL, providing an opportunity for intervention [159, 160, 163]. It is paramount that a careful risk–benefit assessment is done and that proper information is given to the prospective donor, this should also include recommendations on health-promoting behaviour post-donation [164].

Summary of evidence	**LE**
A systematic review and meta-analysis on complications in minimally invasive LDN concluded that the techniques used for minimally invasive LDN are safe and associated with low complication rates.	1a
Survival rates and risk of end-stage renal disease are similar to those in the general population whilst donors HRQoL remains on average better than the general population.	2b

Recommendations	**Strength rating**
Restrict living donor nephrectomy to specialised centres.	Strong
Offer long-term follow-up to all living kidney donors.	Strong

*3.1.7 **Recipient complications***

3.1.7.1 General complications

Surgical complications during and after kidney transplantation may expose the recipient to an increased risk of morbidity and mortality. The incidence and management of such complications is therefore of primary importance [137, 144, 165-177]. We herein describe in detail the most common surgical complications in renal transplantation.

3.1.7.2 Haemorrhage

Haematomas are usually a minor complication in renal transplantation. Their incidence is reported to be between 0.2-25% [178, 179]. Small and asymptomatic haematomas do not usually require any intervention. In case of larger haematomas, clinical signs and symptoms due to external pressure with graft dysfunction and/or thrombotic graft vessel complications can be present. These cases may be treated by percutaneous drainage under computed tomography (CT) or ultrasound (US) guidance or may require surgical treatment [178].

3.1.7.3 Arterial thrombosis

Transplant renal artery thrombosis is a rare complication with a prevalence ranging from 0.5-3.5% [180]. Usually, it is a consequence of a technical error during the anastomosis although other causes may be related to both the donor and recipient's artery condition (i.e. atherosclerosis), intimal rupture during kidney harvesting, acute rejection episodes, external compression by haematoma or lymphocele, hypercoagulative state, severe hypotension, and toxicity of immunosuppressive agents (cyclosporine or sirolimus) [181]. The clinical manifestations are acute reduction of urine output and the elevation of renal function tests, often resulting in graft loss [178]. The diagnosis is obtained with eco-colour-Doppler [178]. Surgical exploration is usually recommended to evaluate the status of the graft. In the rare event the graft appears salvageable, a thrombectomy must be performed. In this situation, the iliac artery is clamped and an arteriotomy vs. a dissection of the vascular anastomosis must be performed in order to remove the clot. The graft can be flushed in-situ and re-vascularised [178]. Unfortunately, in the majority of the situations, the graft is not perfused and therefore an allograft nephrectomy must be performed [178, 182]. Alternatively, thrombolytic agent administration through a catheter directly into the transplant renal artery can be an efficient treatment, after the first ten to fourteen post-transplantation days [178].

Summary of evidence	**LE**
The diagnosis of renal artery thrombosis depends on eco-colour-Doppler followed by surgical exploration to assess the status of the graft.	2b
Thrombectomy in the case of a viable graft and allograft nephrectomy in the case a non-viable graft are the treatment options for renal artery thrombosis.	2b

Recommendations	Strength rating
Perform ultrasound-colour-Doppler in case of suspected graft thrombosis.	Strong
Perform surgical exploration in case of ultrasound finding of poor graft perfusion.	Strong
Perform a surgical thrombectomy in case of a salvageable graft if arterial thrombosis is confirmed intra-operatively.	Weak
Perform an allograft nephrectomy in case of a non-viable graft.	Strong

3.1.7.4 Venous thrombosis

Transplant renal vein thrombosis is an early complication (prevalence 0.5-4%) and one of the most important causes of graft loss during the first post-operative month [183]. The aetiology includes technical errors and/or difficulties during surgery [178] and the hypercoagulative state of the recipient [184, 185]. Colour-Doppler-flow-ultrasonography shows absence of venous flow with an abnormal arterial signal (usually a plateau-like reversed diastolic flow). Furthermore, it is common to see an enlargement of the graft due to venous congestion [186]. Surgical exploration is usually recommended despite the fact that the majority of the cases will result in graft loss. In those cases where the venous thrombosis has not resulted in kidney loss at surgical exploration, a venotomy with surgical thrombectomy after clamping the iliac vein can be performed. Alternatively, an explantation and subsequent re-implantation can be considered [178]. Thrombolytic agents can also be used; however, their results have not been satisfactory [178, 187, 188].

Summary of evidence	LE
The diagnosis of renal vein thrombosis depends on colour-Doppler-flow-ultrasonography followed by surgical exploration to assess the status of the graft.	2b
Thrombectomy in the case of a viable graft and allograft nephrectomy in the case a non-viable graft are the treatment options for renal vein thrombosis.	2b

Recommendations	Strength rating
Perform ultrasound-colour-Doppler in case of suspected graft thrombosis.	Strong
Perform surgical exploration in case of ultrasound finding of poor graft perfusion.	Weak
If venous thrombosis is confirmed intra-operatively, perform a surgical thrombectomy in case of a salvageable graft or an allograft nephrectomy in case of a non-viable graft.	Weak
Do not routinely use pharmacologic prophylaxis to prevent transplant renal vein thrombosis.	Strong

3.1.7.5 Transplant renal artery stenosis.

The incidence of transplant renal artery stenosis is 1-25% [189, 190]. Risk factors include small calibre and atherosclerosis of the donor artery, trauma to donor artery at procurement, absence of arterial patch, suturing technique (interrupted vs. continuous), and damage to the iliac artery during transplantation [191, 192]. It is more common at the site of the anastomosis [191, 192]. It can be suspected in case of arterial hypertension refractory to medical treatment and/or an increase in serum creatinine without hydronephrosis or urinary infection (30). The diagnosis is performed by US-colour-Doppler, showing a peak systolic velocity (PSV) of > 200 cm/s in the graft renal artery [191]. In cases of doubt a magnetic resonance angiogram or a CT angiogram can be performed [193]. It is important to determine whether the stenosis is haemodynamically significant or not. Usually, a stenosis of over 50% is considered a risk for kidney impairment [194]. In case of mild stenosis (< 50%) and absence of symptoms with no deterioration of the allograft, the management is normally conservative; although, a strict follow-up with US-colour-Doppler and clinical parameters has to be adopted due to the possible risk of graft failure [191]. In cases of clinically significant stenosis and/or > 50% on US-colour-Doppler, a confirmatory angiogram should be performed. If confirmed and a decision to treat is taken, treatments include percutaneous transluminal angioplasty/stent or surgical intervention. Interventional radiology is typically the first choice although patients considered unsuitable for radiological angioplasty due to recent transplant, multiple, long and narrow stenosis, or after failure of angioplasty may benefit from surgical treatment [191, 192].

Summary of evidence	LE
Suspect transplant renal artery stenosis in case of refractory arterial hypertension and/or increasing serum creatinine without hydronephrosis/infections.	3
The diagnosis for transplant renal artery stenosis is by US-colour-Doppler, showing a peak systolic velocity (PSV) of > 200 cm/s in the graft renal artery.	2a
Interventional radiology is the first-line treatment option for transplant renal artery stenosis; however, in patients considered unsuitable for radiological angioplasty surgical treatment may be considered.	3

Recommendations	Strength rating
Perform ultrasound-colour-Doppler to diagnose an arterial stenosis, in case of undetermined results on ultrasound consider a magnetic resonance or computed tomography angiogram.	Strong
Perform percutaneous transluminal angioplasty/stent, if feasible, as first-line treatment for an arterial stenosis.	Strong
Offer surgical treatment in case of recent transplant, multiple, long and narrow stenosis, or after failure of angioplasty.	Strong

3.1.7.6 Arteriovenous fistulae and pseudo-aneurysms after renal biopsy

Percutaneous biopsy may result in arteriovenous (AV) fistulae and/or intra-renal pseudo-aneurysms in 1-18% of cases [195]. The aetiology of the AV fistula is related to the simultaneous injury of adjacent arterial and venous branches. A pseudo-aneurysm occurs when only the arterial branch is damaged. Both conditions are diagnosed with US-colour-Doppler [178]. The majority of AV fistulae are asymptomatic, resolving in one to two years spontaneously, whilst approximately 30% of them persist and become symptomatic. Typically, the symptoms are hypertension, haematuria, and graft dysfunction due to shunting between arterial and venous vessels. There is an increased risk of spontaneous rupture in case of enlarging pseudo-aneurysms. For both AV fistulae and pseudo-aneurysm, angiographic selective or super selective embolisation represents the treatment of choice [196]. Partial or radical allograft nephrectomy is currently considered the last option [178].

Recommendations	Strength rating
Perform a ultrasound-colour-Doppler if a arteriovenous fistulae or pseudo-aneurysm is suspected.	Strong
Perform angiographic embolisation as first-line treatment in symptomatic cases of arteriovenous fistulae or pseudo-aneurysm.	Strong

3.1.7.7 Lymphocele

Lymphocele is a relatively common (1-26%) complication [197]. There is a significant aetiological association with diabetes, mammalian target of rapamycin (mTOR) inhibitors (i.e sirolimus) therapy, and acute rejection [198]. For large and symptomatic lymphocele, laparoscopic fenestration is associated with the lowest overall recurrence (8%) and complication (14%) rate compared to open surgery and aspiration therapy [199]. Placement of a percutaneous drain (i.e. Pig-Tail) is an option with a success rate as high as 50% [163]. Percutaneous aspiration can be performed although the recurrence rate can be as high as 95% [199], with an increased risk of local infection (6-17%) [199]. Furthermore, sclerosant agents such as ethanol, fibrin sealant, gentamicin, or octreotide reduce the recurrence rate compared to simple aspiration [199, 200].

Recommendations	Strength rating
Perform percutaneous drainage placement as the first treatment for large and symptomatic lymphocele.	Strong
Perform fenestration when percutaneous treatments fail.	Strong

3.1.7.8 Urinary leak

Urinary leakage occurs in 0-9.3% of cases [201]. Anastomotic urine leaks can be ureteral or vesical [202]. Ureteral necrosis and/or suture failure are the most important causes [203, 204]. Non-technical risk factors include recipient age, number of renal arteries, site of arterial anastomosis, occurrence of acute rejection episodes, bladder problems, and immunosuppressive regimen [205]. Urinary leak can be suspected by the urine output and the creatinine level in the drain fluid [203]. In order to decrease the risk of ureteral necrosis, it is important to preserve vascularisation of the distal ureter [203]. Furthermore, the routine use of a JJ-stent is

recommended [204, 206]. The management of urinary leak depends on the location (renal pelvis, proximal or distal ureter, and bladder), the time of appearance and the volume of the leak. For early and low volume urine leaks the treatment may be conservative (i.e. urethral catheter, percutaneous nephrostomy and JJ-stent) [207]. In case of failure of the conservative management, or massive leak, surgical repair must be undertaken. Ureteral re-implantation directly to the bladder or to the native ureter provide similar results [140, 207].

Summary of evidence	LE
Suspect urinary leakage based on the urine output and the creatinine level in the drain fluid.	3
For early and low volume urine leaks conservative management may be considered.	3
Surgical repair should be undertaken when conservative management fails or massive urine leak occurs.	2b

Recommendations	Strength rating
Manage urine leak by JJ-stent and bladder catheter and/or percutaneous nephrostomy tube.	Strong
Perform surgical repair in cases of failure of conservative management.	Strong

3.1.7.9 Ureteral stenosis

Ureteral stenosis is a common complication in recipients, with an incidence of 0.6-10.5% [208]. Early stenosis (within three months of surgery) is usually caused by surgical technique or compromised ureteral blood supply during surgery. Late stenosis (after > six months) is provoked by infection, fibrosis, progressive vascular disease and/or rejection [203, 209]. Clinically significant ureteral stricture should be considered when persistent hydronephrosis on US occurs in association with impaired renal function. The first approach in the management of stricture is the placement of a percutaneous nephrostomy tube with an antegrade pyelogram [208]. The following treatment options depend mainly on the timing, recoverable kidney function, anatomy of the stricture, patient body habitus/comorbidities, and surgeon preference. Strictures < 3 cm in length may be treated endoscopically either with percutaneous balloon dilation or antegrade flexible ureteroscopy and holmium laser incision. In this scenario the success rate approaches 50%; although, maximum success is obtained for strictures < 1 cm [210-212]. In case of a recurrence after a primary endourological approach and/or stricture > 3 cm in length, surgical reconstruction should be performed [209] including direct ureteral re-implantation, pyelo-vesical re-implantation (with or without psoas hitch and/or Boari Flap) or in cases with a normal native ureter, uretero-ureterostomy [213, 214]. Long-term graft and patient survival are not significantly affected [215].

Summary of evidence	LE
Clinically significant ureteral stricture should be considered when persistent hydronephrosis on US occurs in association with impaired renal function.	3
The first approach in the management of a stricture is the placement of a percutaneous nephrostomy tube with an antegrade pyelogram.	2b
Strictures < 3 cm in length may be treated endoscopically.	3
For strictures > 3 cm in length or those which have reoccurred following a primary endourological approach surgical reconstruction should be performed.	2b

Recommendations	Strength rating
In case of ureteral stricture, place a nephrostomy tube for both kidney decompression and stricture diagnosis via an antegrade pyelogram.	Strong
Manage strictures < 3 cm in length either with surgical reconstruction or endoscopically (percutaneous balloon dilation or antegrade flexible ureteroscopy and holmium laser incision).	Strong
Treat late stricture recurrence and/or stricture > 3 cm in length with surgical reconstruction in appropriate recipients.	Strong

3.1.7.10 Haematuria

The incidence of haematuria ranges from 1-34% [201]. According to the literature, the Lich-Gregoire technique provides the lowest incidence of haematuria. Furthermore, meticulous haemostasis during re-implantation results in minimal bleeding [137, 201, 202]. Bladder irrigation is the first-line treatment. Some cases require cystoscopy with evacuation of clots and/or fulguration of bleeding sites [201].

3.1.7.11 Reflux and acute pyelonephritis

The frequency of vesicoureteral reflux is between 1-86% [201, 216]. Acute graft pyelonephritis occurs in 13% of graft recipients. Patients with lower tract urinary infections and cytomegalovirus (CMV) infection present a higher risk of acute graft pyelonephritis [217]. Endoscopic injection of dextranomer/hyaluronic acid copolymer may be the first approach for treatment of vesicoureteral reflux associated with acute pyelonephritis, with a success rate ranging from 57.9% after the first injection to 78.9% after the second injection [218]. Ureteral re-implantation or pyelo-ureterostomy with the native ureter is a viable second treatment option [213].

Recommendation	Strength rating
Use an endoscopic approach as first-line treatment for symptomatic reflux.	Weak

3.1.7.12 Kidney stones

Urolithiasis occurs in 0.2-1.7% of recipients [219, 220]. The most frequent causes are hyper filtration, renal tubular acidosis, recurrent UTIs, hypocitraturia, hyperuricaemia, hyperuricemia, excessive alkaline urine, persistent tertiary hyperparathyroidism and ureteral strictures [221, 222]. Another risk factor can be urinary anastomosis, with the lowest stone rate using Lich-Gregoir technique [220]. The most frequent clinical signs are fever, increased serum creatinine level, decreased urine output, and haematuria. Pain is usually not referred to due to impaired innervation. A US examination usually provides the diagnosis although a CT of the kidneys, ureters and bladder may be needed to confirm the location and size of the stone [221]. The management depends on the location and size of the stone, and the presence of obstruction. In case of obstructive stones first-line treatment includes placement of a nephrostomy tube, or in some occasions a JJ-stent [223]. Extracorporeal shock wave lithotripsy (ESWL) is usually considered the first approach for stones < 15 mm with stone-free rates varying between 40 and 80% depending on the location of the stone [223]. Ureteroscopy, including antegrade and retrograde approaches, can be considered for stones < 20 mm, with a success rate of up to 67% [139, 220, 224]. For larger stones (> 20 mm), percutaneous nephrolithotomy (PNL) can be offered with high overall effective stone-free rates. In cases of large impacted stones, uretero-ureteral anastomosis, pyelo-ureteral anastomosis, or uretero-vesical re-implantation may provide excellent results for both stone and ureteral obstruction [220].

Summary of evidence	LE
Extracorporeal shockwave lithotripsy should be considered as the first-line treatment option for stones < 15 mm.	2b
Antegrade/retrograde ureteroscopy and percutaneous nephrolithotomy may be considered as treatment options as they provide high stone-free rates.	2b
For larger stones (> 20 mm), PNL can be offered with a high overall effective stone-free rate.	2b

Recommendations	Strength rating
Evaluate the causes of urolithiasis in the recipient.	Strong
Treat ureteral obstruction due to a stone with a percutaneous nephrostomy tube or JJ-stent placement.	Strong
Perform shockwave lithotripsy or antegrade/retrograde ureteroscopy for stones < 15 mm.	Strong
Perform percutaneous nephrolithotomy for stones > 20 mm.	Weak

3.1.7.13 Wound infection

Wound infections occur in about 4% of cases. Risk factors include recipients > 60 years, high BMI, anaemia, hypo-albuminemia, long surgical times (> 200 min) [225]. Bacteria commonly involved are *Enterobacteriaceae, Staphylococcus aureus* and *Pseudomonas* [213]. Subcutaneous sutures, pre-dialysis transplantation, sealing or ligation of lymphatic trunks, prophylactic fenestration, reducing corticosteroid load, and avoiding sirolimus/everolimus therapy can decrease wound complication rates [225].

3.1.7.14 Incisional hernia

Incisional hernia occurs in approximately 4% of open kidney transplantations. Risk factors include age, obesity, diabetes, haematoma, rejection, re-operation through the same transplant incision and use of m-TOR inhibitors. Mesh infection is a risk factor for incisional hernia recurrence [226]. Open and laparoscopic repair approaches are safe and effective [226].

*3.1.8 **Urological malignancy and renal transplantation***

The following section is limited to a synopsis of three systematic reviews conducted by the EAU Renal Transplantation Panel.

3.1.8.1 Malignancy prior to renal transplantation

3.1.8.1.1 In the recipient

Standard procedure for transplant candidates includes systematic screening for the presence of any active/latent cancer or a past history of cancer. In candidates with a previous history of urological cancer, it can be challenging to decide if patients are suitable for transplantation and if so how long the waiting period prior to transplantation should be. To date, the waiting period has been primarily based on the Cincinnati Registry, which takes into account the type of tumour and the time between its treatment and kidney transplantation. However, the Cincinnati Registry has potential drawbacks as it does not consider the epidemiology of tumours or that diagnostic and therapeutic procedures/tests have changed over time and that prognostic tools have improved. Additionally, treatment and the staging of the disease are not defined.

According to a recent systematic review the risk of tumour recurrence was similar between transplantation (n=786) and dialysis (n=1,733) populations for renal cell carcinoma (RCC) and prostate cancer (PCa). This was especially true for low grade/stage PCa, for which the risk of recurrence was low and consistent with nomograms [227]. For low stage/grade RCC the recurrence rate was significant for both dialysis and renal transplantation; however, recurrences were actually contralateral RCC with no impact on patient or graft survival [227].

Testicular cancer had a low risk of recurrence but case reports highlighted the possibility of late recurrence even for stage I tumours [227].

For urothelial carcinoma, studies were mainly related to upper urinary tract carcinomas in the context of aristolochic acid nephropathy for which the rate of synchronous bilateral tumour was 10-16% and the rate of contralateral recurrence was 31-39% [227].

These findings imply that a kidney transplant candidate with a history of appropriately treated low stage/grade PCa (PSA ≤ 10, Gleason score ≤ 6 and T1/T2a) or low grade T1 RCC could be listed for renal transplantation without any additional delay compared to a cancer-free patient. However, as the level of evidence was low, more studies are needed to standardise waiting periods before renal transplantation.

Summary of evidence	**LE**
Renal Cell Carcinoma	
The recurrence rates for transplanted vs. dialysed patients at <1, 1–5, and > 5 years were 0–8% vs. 0%, 0–27% vs. 0–9% and 0–41% vs. 0–48%, respectively.	2b
Overall five year survival rates for transplantation vs dialysed patients were 80–100% vs. 76–100%, respectively.	
Prostate Cancer	
The recurrence rates for transplantation patients at <1 and > 5 years were 0–9% and 4–20%, respectively.	2b
Overall, 1–5 year survival rates for transplantation patients ranged from 62% to 100%.	

Recommendation	**Strength rating**
List for renal transplantation patients with a history of appropriately treated low stage/grade renal cell carcinoma or prostate cancer without additional delay.	Weak

3.1.8.1.2 In the potential donor kidney

In the general population, RCC constitutes 3% of all malignancies, with the incidence being highest in patients aged > 60 years. The current increasing age of donors may lead to a higher number of incidental RCCs found in donor kidneys and could theoretically decrease the number of kidneys suitable for transplantation. The main surgical approach to these kidneys is ex vivo tumour excision on the back-table with an oncological margin, frozen section biopsy, bench surgery renorraphy, and finally transplantation in the conventional fashion [228].

A systematic review assessed the effectiveness and harms of using kidneys with small renal tumours, from deceased or living donors, as a source for renal transplantation and it reported that five year overall and graft survival rates were 92% and 95.6%, respectively [228]. Tumour excision was performed ex-vivo in all cases except for two (107/109 patients), and the vast majority of excised tumours were RCCs (88/109 patients), with clear-cell subtype the most common [228]. This systematic review, although with low-level evidence, suggested that kidneys with small renal masses are an acceptable source for renal transplantation and do not compromise oncological outcomes with similar functional outcomes to other donor kidneys.

Summary of evidence	**LE**
Tumour excision was performed *ex-vivo* in all cases except for two (107/109 patients).	2b
Overall survival rates at one, three and five years were 97.7%, 95.4%, and 92%, respectively.	
Mean graft survival rates at one, three and five years were 99.2%, 95%, and 95.6%, respectively.	

Recommendation	**Strength rating**
Do not discard a kidney for potential transplantation on the basis of a small renal mass alone.	Weak

3.1.8.2 Malignancy after renal transplantation

Cancer development after kidney transplant has become a major problem as it is one of the main causes of death in this population. Urological cancers, have an increased incidence after kidney transplantation partly due to the increasing age of recipients and their prolonged survival after transplantation.

Treatment of localised PCa following kidney transplantation is challenging due the presence of the kidney graft in the pelvic cavity close to the prostate. Two systematic reviews reported that oncological outcomes following PCa treatment in kidney transplant recipients are comparable to the non-transplanted population [229, 230] and surgery (radical prostatectomy), carried out in tertiary high-volume referral centres was the treatment choice in 75 to 85% of patients [229, 230]. Marra *et al.,* reported cancer-specific survival rates of 96.8% for surgery, 88.2% for radiotherapy with androgen deprivation therapy and 100% for brachytherapy at mean follow-up of 24 months [230]. Hevia *et al.,* reported five year cancer-specific survival of 97.5% for surgery, 87.5% for external beam radiation and 94.4% for brachytherapy [229].

Summary of evidence	**LE**
Surgery (radical prostatectomy) was the most frequently performed treatment for localised PCa after kidney transplant.	2b
Overall oncological outcomes following PCa treatment in kidney transplant recipients were comparable to the non-transplanted population.	2b

Recommendations	**Strength rating**
Be aware of the presence of a kidney transplant in the pelvis and the possibility of subsequent transplants when planning treatment for prostate cancer.	Strong
Refer kidney transplant patients with prostate cancer to an integrated transplant urology centre.	Strong

3.1.9 ***Matching of donors and recipients***

Histocompatibility antigens show remarkable polymorphism and human leukocyte antigen (HLA) matching is still very important in kidney transplantation as transplant outcome correlates with the number of HLA mismatches [231-234]. Human leukocyte antigen incompatibility can result in proliferation and activation of the recipient's CD4+ and CD8+ T-cells with concomitant activation of B-cell allo-antibody production. This may lead to cellular and humoral graft rejection. Matching should concentrate on HLA antigens, which impact

outcome. Human leukocyte antigens A, B, C as well as DR must be determined in all potential recipients and donors according to current guidelines and national allocation rules [231-236]. Additionally, it is recommended to determine HLA-DQ antigens of donor and recipient. Furthermore, HLA-DP antigen characterisation may be performed, especially for sensitised recipients [231-236].

All patients registered for renal transplantation must have their serum screened for anti-HLA antibodies, which are particularly common after pregnancy, previous transplant, transplant rejection, and blood transfusions [231-236]. Thorough pre-transplant testing for HLA antibodies must be performed according to current recommendations [231-236]. Sera from potential organ recipients should be screened for HLA-specific antibodies every three months or as stipulated by the national and/or international organ exchange organisations [231-236]. In addition, screening for HLA-specific antibodies should be carried out at two and four weeks after every immunising event, e.g. blood transfusion, transplantation, pregnancy, and graft explantation [231-236]. Highly sensitised patients should have prioritised access to special allocation programmes [233, 234, 236], such as the acceptable mismatch (AM) programme of Eurotransplant [237]. A careful analysis of HLA antibody specificities must be carried out to avoid unacceptable HLA antigens and to determine acceptable HLA antigens in potential donors, who are expected to give a negative cross-match result. The definition of unacceptable HLA antigens should be implemented according to local allocation rules and international recommendations [231-235, 238]. The information on unacceptable HLA antigens should be highlighted with the patient's details in the database of the national kidney-sharing programme, preventing the unnecessary transport of kidneys to recipients with high antibody sensitivity.

To avoid hyper-acute rejection (HAR), adequate (e.g. CDC, virtual) cross-match tests must be performed before each kidney and combined kidney/pancreas transplantation in accordance with national and international recommendations [231-234, 236].

Laboratories which provide HLA-testing, HLA antibody testing and cross-matching for transplant centres must have valid accreditation to ensure accuracy and reliability [225, 226, 231-233]. They must follow the standards of national and international organisations, such as the European Federation for Immunogenetics [236].

Previously, compatibility for ABO blood group antigens and HLA antigens was of critical importance in kidney transplantation. This may change in the future, e.g. in the new U.S. allocation system A2 and A2B donors are transplanted into B recipients [234]. To avoid an increasing imbalance between demand and supply in deceased donor kidney transplantation in O recipients, ABO identity is demanded by several organ allocation organisations with a few exceptions, e.g. as in zero HLA-A+B+DR-mismatch kidneys [234, 235]. With the introduction of antibody elimination methods, potent immunosuppression and novel agents (e.g. anti B-cell drugs), successful ABO-incompatible living donor transplantations, with good long-term outcomes are possible [239, 240]. However, higher costs and infection rates have been described.

Even the barrier of a positive cross-match due to preformed HLA antibodies is under discussion with newer "desensitisation" techniques available in cases with available living donors [241, 242]. Success rates are lower, antibody-mediated rejections are frequent, but survival may be better compared to waiting list survival on dialysis. While this is a rapidly evolving field, further research is needed to define standard protocols. Until then such "desensitisation" protocols are experimental and patients undergoing "desensitisation" should be treated in specialised centres, where outcomes are documented. Patients should be informed adequately of the risks and limitations and alternative strategies (e.g. acceptable mismatch programmes, cross-over transplantation and donor chains) should be discussed.

Summary of evidence	**LE**
Human leukocyte antigen matching is very important in kidney transplantation as transplant outcome correlates with the number of HLA mismatches. Matching should concentrate on HLA antigens, which impact outcome.	3
In accordance with national and international recommendations adequate (e.g. CDC, virtual) cross-match tests must be performed before each kidney and combined kidney/pancreas transplantation to avoid hyper-acute rejection.	3

Recommendations	Strength rating
Determine the ABO blood group and the human leukocyte antigen A, B, C and DR phenotypes for all candidates awaiting kidney transplantation.	Strong
Test both the donor and recipient for human leukocyte antigen DQ. Human leukocyte antigen DP testing may be performed for sensitised patients.	Strong
Perform thorough testing for HLA antibodies before transplantation.	Strong
Perform adequate cross-match tests to avoid hyper-acute rejection, before each kidney and combined kidney/pancreas transplantation.	Strong

3.1.10 Immunosuppression after kidney transplantation

The principle underlying successful immunosuppression is 'the balance of survival'. Practitioners must prescribe a dosage of drug high enough to suppress rejection without endangering the recipient's health. Increased understanding of immune rejection has led to the development of safe modern immune suppression agents [243, 244], which suppress sensitised lymphocyte activity against a transplant. Immunosuppression is particularly important during the initial post-transplant period when there is a high incidence of early post-transplant rejection.

In later post-operative stages, 'graft adaptation' occurs, resulting in the very low rejection rates seen in maintenance patients. Rejection prophylaxis should therefore be reduced over time by steroid tapering and gradual lowering of calcineurin inhibitor (CNI) [243-245].

Non-specific side effects of immunosuppression include a higher risk of malignancy and infection, particularly opportunistic infections [243-245]. All immunosuppressants also have dose-dependent specific side effects. Current immunosuppressive protocols aim to reduce drug-specific side effects using a synergistic regimen. A truly synergistic regimen allows profound dose reductions of immunosuppressive drugs; therefore, reducing side effects whilst still maintaining efficacy due to the synergistic effects of the immunosuppressants.

The currently recommended standard initial immunosuppression regime provides excellent efficacy with good tolerability [243-246]. It is given to most patients and consists of:

- calcineurin inhibitors (preferably tacrolimus, alternatively cyclosporine);
- mycophenolate (MMF or enteric-coated mycophenolate sodium [EC-MPS]);
- steroids (prednisolone or methylprednisolone);
- induction therapy (preferably basiliximab in low and standard risk patients and anti-thymocyte globulin (ATG) in high-risk patients).

This multidrug regimen reflects the current standard of care for the majority of transplant recipients worldwide [243-245] and may be modified according to local needs and immunological risk. This standard regimen is likely to change as new immunosuppressive drugs and new treatment regimens are developed [243-245]. In addition, any initial drug regimen will need to be tailored to the individual needs of a patient as suggested by the appearance of side effects, lack of efficacy or protocol-driven requirements.

Recommendation	Strength rating
Perform initial rejection prophylaxis with a combination therapy of a calcineurin inhibitor (preferably tacrolimus), mycophenolate, steroids and an induction agent (either basiliximab or anti-thymocyte globulin).	Strong

3.1.10.1 Calcineurin inhibitors

Both cyclosporine and tacrolimus have significant side effects that are hazardous to the graft and patient [243-250]. Most importantly, both are nephrotoxic [251, 252], and long-term use is an important cause of chronic allograft dysfunction [253], eventually leading to graft loss or severe chronic kidney disease in recipients of non-renal organs. Both CNIs are considered to be 'critical-dose' drugs, so that any deviations from exposure can lead to severe toxicity or failure of efficacy. Because of the narrow therapeutic window and the potential for drug-to-drug interaction, CNIs should be monitored using trough levels, which provide a reasonable estimate for exposure [250].

Meta-analysis of tacrolimus and cyclosporine has demonstrated similar outcomes with respect to overall patient and graft survival [243-249, 254-256]. Tacrolimus provided better rejection prophylaxis and was associated with better graft survival, when censored for death in some analyses. Renal function was favourable for tacrolimus treated patients, in a number of number of trials [254, 257-261]. Therefore, both CNIs can be used

for the effective prevention of acute rejection, but due to higher efficacy tacrolimus is recommended by current guidelines as first-line CNI [244].

For both CNIs several different formulations are available [250, 262-270]. Tacrolimus once-daily dosing seems to be preferred by patients and is associated with better adherence and lower pharmacokinetic variability [250, 271, 272]. Precautions (e.g. close surveillance and determination of drug levels) should be instituted after conversion from one formulation to another [270, 273-277]. In case of specific side effects of a CNI (e.g. hirsutism, alopecia, gingival hyperplasia, diabetes, polyoma nephropathy) conversion to another CNI can be a successful strategy to reduce side effects [243-245, 278]. Due to differences in the efficacy and safety profile, the choice of CNI should include the individual risks and benefits for each patient.

Despite their side effects, CNIs have been a cornerstone of modern immunosuppressive regimens for more than thirty years as they have resulted in an exemplary improvement in kidney graft survival [243, 244]. Future protocols aim to minimise or even eliminate CNIs [245, 248, 250, 279-282]. However, until such strategies provide superior outcomes, CNIs remain the standard of care [243, 244, 283]. For severe CNI-related side effects, CNI withdrawal, replacement, or profound reduction may be needed [243, 245, 248, 279, 280]. Special attention should be paid to maintenance patients, who may need less CNIs than previously thought [243, 245, 250, 280, 281, 284].

Summary of evidence	**LE**
Meta-analysis of tacrolimus and cyclosporine has demonstrated similar outcomes with respect to overall patient and graft survival however, tacrolimus provided better rejection prophylaxis and renal function.	1a
Due to differences in the efficacy and safety profile, the choice of CNI should take into account the immunological risk, characteristics, concomitant immunosuppression, and socio-economic factors of the recipient.	1

Recommendations	**Strength rating**
Use calcineurin inhibitors for rejection prophylaxis as they represent current best practice pending publication of long-term results using newer agents.	Strong
Use tacrolimus as first-line calcineurin inhibitor due to its higher efficacy.	Strong
Monitor blood-levels of both cyclosporine and tacrolimus to allow appropriate dose adjustment of calcineurin inhibitors.	Strong

3.1.10.2 Mycophenolates (MPA)

The mycophenolates, MMF and EC-MPS, are based on mycophenolic acid, which inhibits inosine monophosphate dehydrogenase (IMPDH) [285-289]. This is the rate-limiting step for the synthesis of guanosine monophosphate in the *de novo* purine pathway. As the function and proliferation of lymphocytes is more dependent on *de novo* purine nucleotide synthesis compared to other cell types, IMPDH inhibitors may provide more specific lymphocyte-targeted immunosuppression. The co-administration of mycophenolate with prednisolone and CNI has resulted in a profound reduction of biopsy-proven rejections [243, 246, 285-289]. Mycophenolic acid is not nephrotoxic; however, it inhibits bone marrow function and may cause CMV infections and gastrointestinal side effects, particularly diarrhoea [243, 246, 285-289]. There is also a higher incidence of polyoma nephropathy, especially when mycophenolate is combined with tacrolimus [290].

Both MPA formulations are equally effective with an almost identical safety profile [241, 280, 283, 285-288], though some prospective studies suggest a better gastrointestinal side-effect profile for EC-MPS in patients who have suffered from MMF-related gastrointestinal complaints, although firm evidence from prospective randomised studies is lacking [285-289, 291].

Mycophenolic acid is recommended by guidelines [244]. Standard doses in combination with cyclosporine are MMF 1 g or EC-MPS 720 mg twice daily, although higher initial doses have been suggested [243, 244, 285-289]. Despite its frequent use with tacrolimus, there is insufficient evidence to support the optimal dosage for this combination [243, 285, 287, 288, 292]. Tacrolimus has no influence on MPA exposure and leads to approximately 30% higher MPA exposure compared to cyclosporine. Most transplant centres use the same starting dose as in cyclosporine-treated patients, however dose reductions are frequent, especially because of gastrointestinal side effects. Weak evidence suggests that MPA dose reductions are associated with inferior

outcomes, especially in cyclosporine treated patients [286-288, 293, 294]. Due to the high incidence of side effects, some centres perform a protocol-driven MPA dose reduction in tacrolimus treated patients [285, 287]. Regular monitoring for polyoma (BK virus) is recommended in patients given MPA combined with tacrolimus [243, 290].

Due to a higher incidence of CMV disease with MPA [289], either CMV prophylaxis or a pre-emptive strategy with regular screening for CMV viraemia should be instituted [243, 295]. Cytomegalovirus prophylaxis with antiviral medications (e.g. valganciclovir) should be used routinely in CMV positive recipients and in CMV negative recipients of CMV positive organ transplants, because prophylaxis has recently been shown to reduce CMV disease, CMV-associated mortality in solid organ transplant recipients, and leads to better long-term graft survival in kidney allograft recipients.

The benefit for MPA drug monitoring is uncertain and currently not recommended for the majority of patients [285, 287, 288, 296].

In maintenance patients, the potency of MPA can be used for successful steroid withdrawal in most patients [297] or for substantial dose reductions of nephrotoxic CNIs, which may lead to better renal function [243-246, 248, 280, 298]. Although there have been several studies of the potential for CNI-free protocols with MPA and steroids, complete CNI avoidance or withdrawal over the first three years has been associated with a substantially increased rejection risk and even worse outcomes in prospective randomised studies [243, 245, 280]. In contrast, CNI withdrawal under MPA and steroids appeared to be safe in long-term maintenance patients beyond five years post-transplant and resulted in improved renal function [243, 245, 248, 280, 298, 299].

Summary of evidence	**LE**
The co-administration of MPA with prednisolone and CNI has resulted in a profound reduction of biopsy-proven rejections.	1
Both MPA formulations, MMF and EC-MPS, are equally effective with an almost identical safety profile.	1
Due to a higher incidence of CMV disease with MPA either CMV prophylaxis or a pre-emptive strategy with regular screening for CMV viraemia should be instituted	1

Recommendation	**Strength rating**
Administer mycophenolate as part of the initial immunosuppressive regimen.	Strong

3.1.10.3 Azathioprine

Mycophenolate is now routinely used as a primary therapy in place of azathioprine in most units worldwide. In comparison to azathioprine, mycophenolate reduced rejection rates significantly in prospective randomised trials [243, 244, 246, 285-289]. Although a large, prospective study found that azathioprine may give acceptable results in a low-risk population [300], azathioprine is usually reserved for patients who cannot tolerate MPA [243, 244, 285, 286, 288]. When added to dual therapy with cyclosporine and steroids, a meta-analysis found no significant benefit for azathioprine with respect to major outcome parameters [301].

Recommendation	**Strength rating**
Azathioprine may be used in a low-risk population as an immunosuppressive drug, especially for those intolerant to mycophenolate formulations.	Weak

3.1.10.4 Steroids

Steroids have a large number of side effects [243-245, 297], especially with long-term use. Most practitioners still consider steroids (either prednisolone or methylprednisolone) to be a fundamental adjunct to primary immunosuppression, even though successful steroid withdrawal has been achieved in the vast majority of patients in many prospective, randomised trials [243, 245, 246, 297, 302, 303]. The risk of steroid withdrawal depends on the use of concomitant immuno-suppressive medication, immunological risk, ethnicity, and time after transplantation. Although the risk of rejection diminishes over time, potential benefits may be less prominent after a prolonged steroid treatment period [243-246, 297]. Recent studies suggest similar efficacy but less diabetes after early steroid withdrawal or steroid minimisation in low risk patients treated with tacrolimus, MPA and induction (either basiliximab or ATG) [304, 305].

Recommendations	Strength rating
Initial steroid therapy should be part of immunosuppression in the peri-operative and early post-transplant period.	Strong
Consider steroid withdrawal in standard immunological risk patients on combination therapy with calcineurin inhibitors and mycophenolic acid after the early post-transplant period.	Weak

3.1.10.5 Inhibitors of the mammalian target of rapamycin (m-TOR)

The immunosuppressants, sirolimus and everolimus, inhibit the mammalian target of rapamycin and suppress lymphocyte proliferation and differentiation [243, 279, 306-308]. They inhibit multiple intracellular pathways and block cytokine signals for T-cell proliferation. Similar effects are seen on B-cells, endothelial cells, fibroblasts, and tumour cells. Inhibitors of m-TOR are as effective as MPA when combined with CNIs in preventing rejection [243, 246, 279, 306-309]. However, m-TOR inhibitors exhibit dose-dependent bone marrow toxicity [243, 279, 306-308]. Other potential side effects include hyperlipidaemia, oedema, development of lymphoceles, wound-healing problems, pneumonitis, proteinuria, and impaired fertility. The extensive side effect profile is responsible for inferior tolerability compared to MPA and potential differences in outcome in early years, when higher doses were used [310-315].

To date, no prospective comparative studies have been carried out on the m-TOR inhibitors sirolimus and everolimus [316]. Both m-TOR inhibitors have an almost identical side effect profile and mainly differ in their pharmacokinetic properties [243, 279, 306-308, 317]. Sirolimus has a half-life of about 60 hours, is given once a day and is licensed for prophylaxis in kidney recipients only. Everolimus has a half-life of about 24 hours, is licensed for kidney, liver and heart recipients and is given twice a day. Everolimus is licenced for use with cyclosporine and can be given simultaneously with cyclosporine, while sirolimus should be given four hours after cyclosporine. The pharmacological drug-drug interaction with cyclosporine is far less relevant for tacrolimus, resulting in the need for a higher starting dose of m-TOR inhibitors in combination with tacrolimus [260, 318, 319]. Sirolimus is also licensed in combination therapy with steroids for cyclosporine withdrawal from combination therapy with cyclosporine.

Therapeutic monitoring of trough levels is recommended because of the narrow therapeutic window and the risk of drug-to-drug interactions [243, 279, 306-308, 317].

When combined with CNIs, antimicrobial prophylaxis for Pneumocystis jirovecii pneumonia should be administered for one year following transplantation, e.g. low-dose cotrimoxazole [243, 306-308]. Most importantly, combination therapy with CNIs aggravates CNI-induced nephrotoxicity, although m-TOR inhibitors themselves are non-nephrotoxic [243]. Several studies suggest less favourable outcomes and increased drug discontinuations due to adverse events for this combination, especially if CNIs are maintained at standard dosages [243, 246, 248, 260, 309, 311, 312, 320-325]. Calcineurin inhibitor dosage should therefore be substantially reduced in combination therapy with m-TOR inhibitors, which seems to have no impact on efficacy, due to the highly synergistic potential of this combination therapy [279, 306-308, 314, 317].

Several studies suggest m-TOR inhibitors cannot replace CNIs in the initial phase after transplantation due to lower efficacy and a less favourable side effect profile, particularly wound healing problems and lymphoceles [241, 243, 244, 276, 300, 301, 306, 308, 316]. Other trials suggest that m-TOR inhibitors may replace CNI at later stages, e.g. three months after transplantation, with improvements in renal function, predominately in cyclosporine treated patients [243, 245, 246, 248, 258, 279, 306-308, 311, 312, 314, 326-328]. It is unclear if there is a real benefit in comparison to patients on tacrolimus and MPA [258, 327]. However, there is an increased risk of rejection and development of HLA antibodies [243, 245, 258, 279, 329], which may be offset by the benefit of the non-nephrotoxic immunosuppression. Patients treated with m-TOR inhibitors develop less leucopenia and opportunistic viral infections, especially less CMV infections compared to MPA [260, 311, 314, 324-326, 330].

Proteinuria and poor renal function at conversion are associated with inferior outcomes [243, 245, 279, 306-308]. Conversion from CNIs is not advisable in patients with proteinuria > 800 mg/day, and a cautious and individual approach should be followed in patients with GFR < 30 mL/min.

Due to an anti-proliferative effect and a lower incidence of malignancy in m-TOR inhibitor treated patients, conversion from CNIs to m-TOR inhibitors may be beneficial for patients, who develop malignancy after transplantation, or who are at a high risk for the development of post-transplant malignancy or skin cancer [243, 245, 279, 306-308, 313-315, 331-334]. Several studies and case reports have suggested that patients with Kaposi sarcoma under CNI therapy benefit from conversion to an m-TOR inhibitor [332].

In summary, m-TOR inhibitors are not recommended as initial immunosuppressive therapy due to their side effect profile and higher discontinuation rates [244]. However, m-TOR inhibitors are a well-studied alternative treatment option.

Summary of evidence	LE
Combination therapy with CNIs aggravates CNI-induced nephrotoxicity. Therefore, CNI dosage should be substantially reduced in combination therapy with m-TOR inhibitors, which seems to have no impact on efficacy, due to the highly synergistic potential of this combination therapy.	1
Take into consideration impaired wound healing and prophylactic surgical measures when m-TOR inhibitors are used as part of the initial immunosuppressive regimen or when patients treated with m-TOR inhibitors undergo major surgery.	1
When combined with CNIs, antimicrobial prophylaxis for *P. jirovecii* pneumonia should be administered for one year following transplantation.	1
Conversion from CNIs is not advisable in patients with proteinuria > 800 mg/day, and a cautious and individual approach should be followed in patients with GFR < 30 mL/min.	1

Recommendations	Strength rating
The m-TOR inhibitors may be used to prevent rejection in patients who are intolerant to standard therapy.	Weak
Significantly reduce calcineurin inhibitor dosage in a combination regimen with m-TOR inhibitors to prevent aggravated nephrotoxicity.	Strong
Do not convert patients with proteinuria and poor renal function to m-TOR inhibitors.	Strong
Monitor blood-levels of both sirolimus and everolimus to allow for appropriate dose adjustment.	Strong

3.1.10.6 Induction with Interleukin-2 receptor antibodies

Basiliximab, a high-affinity anti-interleukin-2 (IL-2) receptor monoclonal antibody is approved for rejection prophylaxis following organ transplantation [243, 244, 246, 335-339]. Basiliximab is given before transplantation and on day four post-transplant. The drug is safe, and IL-2 receptor antibodies have been shown in RCTs to reduce the prevalence of acute cellular rejection by approximately 40% [243, 244, 246, 335-337]. Meta-analyses [246, 335-337] have confirmed the efficacy, although no positive effect on patient or graft survival could be demonstrated, large retrospective cohort studies and recent large prospective studies suggest such a benefit [243, 244, 340, 341]. Several large controlled trials support the efficacy and safety of quadruple therapy with tacrolimus, mycophenolate and steroids. Interleukin-2 receptor antibodies may allow early steroid withdrawal [297], although higher rejection rates were described in some studies. Most importantly, IL-2 receptor antibodies allow a substantial reduction in CNIs or steroids, while maintaining excellent efficacy and renal function [243-246, 304, 335-337]. Therefore, this regimen is proposed as first-line immunosuppression in patients with low to normal immunological risk [244, 341].

Recommendation	Strength rating
Use interleukin-2 receptor antibodies for induction in patients with normal immunological risk in order to reduce incidence of acute rejection.	Weak

3.1.10.7 T-cell depleting induction therapy

Prophylactic immunosuppression regimens in many countries, particularly the U.S., use potent T-cell depleting 'induction' treatments [243, 244, 246, 335, 340, 342-345]. Most frequently, ATG is used for prevention of rejection in immunological high-risk patients, as supported by meta-analysis [341], and recommended by guidelines [244, 346]. In addition, these potent biological agents are used for the treatment of severe, steroid resistant rejection episodes [342, 345].

Use of T-cell depleting antibodies in immunological low-risk patients has not been associated with improved long-term outcomes but with an increased risk of severe opportunistic infections and malignancy, particularly post-transplant lymphoproliferative disease [243, 244, 246, 335, 341-343]. Some centres use these agents to provide effective rejection prophylaxis in order to facilitate steroid withdrawal [304, 340, 344].

Recommendation	Strength rating
T-cell depleting antibodies may be used for induction therapy in immunologically high-risk patients.	Weak

3.1.10.8 Belatacept

Belatacept is a fusion protein, which effectively blocks the CD28 co-stimulatory pathway and thereby prevents T-cell activation [279, 347-350]. Belatacept is intravenously administered and indicated for use as part of a CNI-free regimen together with basiliximab induction, mycophenolate, and corticosteroids. Long-term data from three randomised studies of *de novo* kidney transplant recipients demonstrated better renal function versus cyclosporine-based immunosuppression, although rates and grades of acute rejection were higher for belatacept in the first year post-transplant [243, 246, 259, 279, 349-355]. In patients receiving a standard deceased or living donor kidney, better graft survival was observed, while similar graft survival rates were found with ECDs. Interestingly, belatacept-treated patients had better preserved histology and developed less donor specific antibodies (DSA) compared to cyclosporine [356]. The long-term safety profile of belatacept treated patients was similar to cyclosporine controls, less belatacept treated patients developed metabolic complications or discontinued treatment due to adverse events [347, 348]. In addition, the option of converting patients (either stable patients or due to CNI or m-TOR associated toxicity) was explored with promising initial results [347, 348, 352, 357-359]. Specific safety signals include a higher rate of post-transplant lymphoproliferative disorder (especially in Epstein-Barr virus (EBV) negative patients), more herpes infections, and tuberculosis in patients from endemic areas [279, 347-350]. Belatacept was approved in the U.S. and in Europe for EBV positive patients, but is not yet available in many countries. Additional studies are ongoing to fully explore the value of this compound.

Recommendation	Strength rating
Belatacept may be used for immunosuppressive therapy in immunologically low-risk patients, who have a positive Epstein-Barr virus serology.	Weak

3.1.11 ***Immunological complications***

Immunological rejection is a common cause of early and late transplant dysfunction [244, 360-364]. There is great variation in the timing and severity of rejection episodes and how they respond to treatment. Today two main types of immunological reactions are distinguished, T-cell mediated rejections (TCMR) and antibody-mediated rejections (ABMR) [244, 360-362, 365]. Antibody-mediated rejection and TCMR may be diagnosed together, called mixed acute rejection. Antibody-mediated rejection may occur as hyperacute rejection (HAR), active rejection or chronic rejection. Chronic ABMR is considered as one of the leading causes of late graft loss.

The ultimate standard for the diagnosis of rejection is transplant biopsy [244], because it is impossible to differentiate acute rejection solely on clinical indicators from other causes of renal dysfunction (e.g. acute tubular necrosis, infection, disease recurrence or CNI nephrotoxicity). Therefore, all rejections should be verified by renal biopsy and biopsies should be classified according to the most recent Banff criteria [366], which are the basis for prognosis and treatment [242, 360, 363]. Renal transplant biopsy should be conducted preferably under US control, using an automated needle biopsy system (e.g. Tru-Cut biopsy gun) [244, 360] with a 16 G needle to assure specimen adequacy. The biopsy procedure is considered safe but complications such as bleeding and AV fistulas may occur [244, 367, 368]. The reported risk of major complications (including substantial bleeding, macroscopic haematuria with ureteric obstruction, peritonitis or graft loss) is approximately 1%. Most important contraindications are anti-coagulant therapy including anti-platelet agents and uncontrolled hypertension.

Summary of evidence	LE
There must be routine access to US-guided biopsy of the transplant and sufficient expertise in the hospital pathology department to allow a rapid and clear-cut diagnosis of rejection or other type of allograft dysfunction.	2
Steroid treatment for rejection may start before the renal biopsy is performed.	2

Recommendations	Strength rating
Monitor transplant recipients for signs of acute rejection, particularly during the first six months post-transplant.	Strong
Take regular blood samples in addition to regular monitoring of urine output and ultrasound examinations in order to detect graft dysfunction during hospitalisation.	Strong
Immediately rule out other potential causes of graft dysfunction in cases of suspected acute rejection. An ultrasound of the kidney transplant should be performed.	Strong
Perform a renal biopsy, graded according to the most recent Banff criteria, in patients with suspected acute rejection episodes.	Strong
Only if contraindications to renal biopsy are present, can 'blind' steroid bolus therapy be given.	Strong
Test patients who suffer acute rejection as soon as possible for anti-HLA antibodies against the graft.	Strong
Reassess the immunosuppressive therapy of all patients with rejection, including patient adherence to the medication, which is of particular importance in late rejections.	Strong

3.1.11.1 Hyper-acute rejection

Hyper-acute rejection is the most dramatic and destructive immunological attack on the graft [231, 244, 360, 361]. It results from circulating, complement-fixing IgG antibodies, specifically reactive against incompatible donor antigen, which engages with and destroys the vascular endothelium within minutes or hours after vascularisation. It occurs in ABO-incompatible grafts due to the presence of high titres of pre-existing iso-antibodies against blood group antigens. In ABO-matched grafts, HAR is mediated by anti-donor HLA IgG antibodies. With the development of the cross-match test before transplantation, HAR has become an extremely uncommon complication [231]. Imaging and histology reveals generalised infarction of the graft, which has to be treated by graft nephrectomy. Therefore, prevention is crucial, either by avoidance of high iso-antibodies against incompatible blood group antigens in case of an ABO-incompatible renal transplant and/or by performing a regular cross-match before transplantation (see section 3.1.8).

Recommendation	Strength rating
Prevent hyper-acute rejection by adequate ABO blood group and human leukocyte antigen matching of donor and recipients.	Strong

3.1.11.2 Treatment of T-cell mediated acute rejection

As only a few randomised trials have investigated different treatment options for this clinical problem, therapy is mainly based on empirical experience rather than on clinical evidence [244, 345, 360, 369]. Parenteral methylprednisolone (500 mg to 1 g) should be given intravenously as one pulse per day for three days. Anuria or a steep rise in the serum creatinine may indicate steroid-refractory rejection and the need for another three day course of pulsed methylprednisolone therapy [244, 360]. In addition, baseline immunosuppression should be optimised to ensure adequate drug exposure [244, 360, 369]. In severe rejection, a conversion from cyclosporine to tacrolimus and/or from azathioprine to mycophenolate is recommended [244, 360].

T-cell depleting biological agents, such as ATG may be given in severe steroid-refractory cases [244, 342, 345, 360, 369]. If biological agents are used, other immunological suppression should be adapted and daily T-cell monitoring should be considered to minimise the dose of the biological agent [342]. Before immunosuppression is intensified, especially before the use of T-cell depleting agents, the prognosis of the graft should be critically assessed against the risks of the aggravated immunosuppression. The patient should be counselled adequately.

Recommendations	Strength rating
Use steroid bolus therapy as first-line treatment for T-cell mediated rejection in addition to ensuring adequate baseline immunosuppression.	Strong
In severe or steroid-resistant rejection, use intensified immunosuppression, high-dose steroid treatment, and eventually T-cell depleting agents.	Strong

3.1.11.3 Treatment of antibody mediated rejection (ABMR)

Treatment of ABMR relies mainly on retrospective studies and empirical treatment guidelines [370]. Consensus is that it is important to classify the clinical and histological phenotype of the rejection in order to make adequate treatment decisions [370]. Important clinical factors are time of rejection (early acute < 30 days posttransplant vs. late), preformed vs. *de novo* donor-specific antibodies (DSA), and histology (active vs. chronic rejection).

For active ABMR due to pre-existing DSA treatment with a steroid bolus (at least three days of 500 mg/day) in combination with intravenous immunoglobulin (IVIG) and plasmapheresis or immune-adsorption is recommended. Intravenous immunoglobulin (IVIG) [244, 360, 371-376] may modulate and/or suppress antibody production. Intravenous immunoglobulin alone seems insufficient for effective treatment and IVIG is used today in a multimodal regimen. Dosages vary widely from 0.2-2.0 g/kg bodyweight, and no comparative studies (e.g. on the dose or optimal concomitant immunosuppression) have been published. Retrospective and prospective case series clearly suggest efficacy of antibody removal using plasmapheresis or immune-adsorption columns [244, 360, 371-376], although details of the procedures vary widely. Adjunctive therapies such as complement inhibitors, rituximab or splenectomy might be considered in severe early acute cases. Despite controversial data on the utility of anti-CD20 antibody [244, 345, 360, 371-376], rituximab may also be considered as adjunctive therapy in late active ABMR according to expert consensus. Although T-cell depleting agents such as ATG appear to have limited value they are frequently used during mixed acute rejection [241]. However, retrospective series suggests aggravated toxicity, when rituximab is combined with ATG [377], or steroids [345]. Furthermore, many centres will optimise maintenance therapy with mycophenolate and steroids and sufficient tacrolimus trough levels should be achieved [244, 360, 371-373, 376].

Chronic AMR due to pre-existent DSA has no specific treatment recommendations except for optimisation of maintenance therapy and eventually IVIG as an adjunctive treatment with a low level of evidence. In patients presenting with *de novo* DSA optimisation of maintenance immunosuppression is recommended and non-adherence should be addressed and managed accordingly. If histology shows active ABMR plasmapheresis, rituximab and IVIG can be considered as potential adjunctive agents without good evidence from clinical trials. If biopsy demonstrates pure chronic ABMR no special treatment is recommended due to lack of convincing data, except for IVIG as potential treatment option without firm evidence. Treatment for chronic ABMR appears to be less successful [360, 371, 373].

In summary, several regimens have proven some efficacy in ABMR. However, except for a beneficial effect of early antibody removal, the lack of firm evidence does not permit evidence-based recommendations for treatment. As a consequence, prevention of ABMR by adequate pre-transplant screening, regular DSA monitoring, avoidance of suboptimal immunosuppression and reinforcement of adherence are crucial [231, 360, 375, 378].

Recommendation	Strength rating
Treatment of antibody mediated rejection should include antibody elimination.	Strong

*3.1.12 **Follow-up after transplantation***

Long-term graft function is of critical importance for the success of a transplant [244, 245]. Therefore, regular long-term follow-up by experienced transplant physicians is essential in order to detect complications or graft dysfunction early and reassure adherence to the immunosuppressive regimen. Complications of immunosuppression occur frequently including specific complications of the different drugs as well as over immunosuppression (namely opportunistic infections and malignancy) [244, 245]. The risk of cancer and cardiac disease is several-fold higher in transplanted patients than in the general population. Cancer is a cause of significant morbidity and mortality in the transplanted population [244, 379, 380]. Cardiovascular disease is the most frequent cause of death in renal allograft recipients [244, 381, 382]. Other important long-term problems are non-adherence [383], the development of anti-HLA antibodies, recurrence of the original disease and CNI associated nephrotoxicity [244, 245].

3.1.12.1 Chronic allograft dysfunction/interstitial fibrosis and tubular atrophy

Many patients lose their grafts due to chronic allograft dysfunction [244, 245, 384]. Histology will usually reveal a chronic process of interstitial fibrosis and tubular atrophy (IF/TA) [385]. Some patients will have immunological chronic ABMR [386], as discussed in section 3.1.11.3. Interstitial fibrosis and tubular atrophy takes months or years to develop and is heralded by proteinuria and hypertension, with a simultaneous or delayed rise in serum creatinine level over months [244, 384, 385]. It is likely that IF/TA is more common in patients who have had

early attacks of acute rejection or infection. The main differential diagnosis is chronic nephrotoxicity [387], which is common in patients receiving CNIs, and pre-existing and/or aggravated chronic kidney damage from a marginal donor kidney [244, 384, 385].

Diagnosis is by renal biopsy [244, 384]. In patients diagnosed early, particularly if there is evidence for CNI toxicity, disease progression may be slowed by conversion to a CNI-free regimen [201-203, 263, 264]. Conversion to m-TOR inhibitors is an option for patients without significant proteinuria (< 800 mg/day), but moderate renal function [243-245]. Alternatively, successful conversion to a mycophenolate based regimen has been described, especially in patients beyond the first three years post-transplant [243, 245, 280]. If there is intolerance to m-TOR inhibitors or MPA, conversion to belatacept or an azathioprine-based regimen may be successful, though the higher risk of rejection warrants close surveillance [359]. If the risk of rejection seems too high, another option is substantial reduction of CNI under the protection of MPA [245, 280].

In patients with proteinuria, intervention with an angiotensin converting enzyme inhibitor, or angiotensin II receptor blocker [244, 384] together with tight blood pressure control may slow down renal progression. Other supportive measures include the treatment of hypertension, hyperlipidaemia, diabetes, anaemia, acidosis, and bone disease [244]. However, ultimately, the patient will require another transplant (if fit enough to go on the transplant waiting list) or dialysis therapy.

Summary of evidence	**LE**
Regular long-term follow-up by experienced transplant physicians is essential in order to detect complications or graft dysfunction early and reassure adherence to the immunosuppressive regimen.	4
Annual screening should include a dermatological examination, cardiovascular history and exam, tumour screening (including a nodal examination, faecal occult screening, chest x-ray, gynaecological and urological examination), and an abdominal US, including US of the native and transplanted kidney. If appropriate, further diagnostic tests should be prompted to treat or slow down the progression of any identified complication.	4
In patients diagnosed early with IF/TA, particularly if there is evidence for CNI toxicity, disease progression may be slowed by conversion to a CNI-free regimen. If the risk of rejection seems too high, another option is substantial reduction of CNI under the protection of MPA.	1
Supportive measures should aim to adequately treat the consequences of chronic kidney disease (e.g. anaemia, acidosis, bone disease).	4

Recommendations	**Strength rating**
Provide lifelong regular post-transplant follow-up by an experienced and trained transplant specialist at least every six to twelve months.	Strong
Advise patients on appropriate lifestyle changes, potential complications, and the importance of adherence to their immunosuppressive regimen.	Strong
Regularly monitor (approximately every four to eight weeks) serum creatinine, estimated glomerular filtration rate, blood pressure, urinary protein excretion, immunosuppression and complications after renal transplantation. Changes in these parameters over time should trigger further diagnostic work-up including renal biopsy, a search for infectious causes and anti-HLA antibodies.	Strong
Perform an ultrasound of the graft, in case of graft dysfunction, to rule out obstruction and renal artery stenosis.	Strong
In patients with interstitial fibrosis and tubular atrophy undergoing calcineurin inhibitor (CNI) therapy and/or with histological signs suggestive for CNI toxicity (e.g. arteriolar hyalinosis, striped fibrosis) consider CNI reduction or withdrawal.	Strong
Initiate appropriate medical treatment, e.g. tight control of hypertension, diabetes, proteinuria, cardiac risk factors, infections, and other complications according to current guidelines.	Strong

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5. CONFLICT OF INTEREST

All members of the EAU Renal Transplantation Guidelines Panel have provided disclosure statements on all relationships that they have that might be perceived to be a potential source of a conflict of interest. This information is publically accessible through the EAU website: http://www.uroweb.org/guidelines/. These Guidelines were developed with the financial support of the EAU. No external sources of funding and support have been involved. The EAU is a non-profit organisation, and funding is limited to administrative assistance, travel and meeting expenses. No honoraria or other reimbursements have been provided.

6. CITATION INFORMATION

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