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 (PUC). The aim is to provide practical recommendations on the clinical management of PUC, with a focus on clinical presentation. When the first carcinoma in the urinary tract is detected in the urethra, this is defined as PUC, 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 Sections 6.7.1 and 6.7.5 of the EAU Guidelines on Muscle-invasive and Metastatic Bladder Cancer [MIBC]) [2].

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

1.2 Panel composition

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

1.3 Available publications

A quick reference document (Pocket Guidelines) is available in print, presenting the main findings of the PUC Guidelines. This reference document is an abridged version that may require consultation together with the full text version. All documents are accessible on the EAU Website Uroweb: https://uroweb.org/guidelines/primary-urethral-carcinoma. The most recent scientific summary paper was published in 2020 [3]. An EAU Guidelines App for iOS and Android devices is also available containing the Pocket Guidelines, interactive algorithms and calculators, clinical decision support tools, Guidelines cheat sheets and links to the extended Guidelines.

1.4 Publication history and summary of changes

The PUC Guidelines were first published in 2013. Standard procedure for EAU Guidelines includes an annual assessment of newly published literature in the field to guide future updates. These 2026 PUC Guidelines present a limited update of the 2025 publication.

1.4.1 Summary of changes

For the 2026 PUC 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:

- In Chapter 4, the 9th edition (2025) of the Tumour, Node, Metastasis (UICC/TNM) classification is incorporated.
- In Chapter 6, updates regarding prognostic factors.
- In Section 7.3.6, updated recommendations for multimodal treatment of advanced urethral carcinoma.

2. METHODS

2.1 Data identification

For the 2026 PUC Guidelines, new and relevant evidence has been identified, collated and appraised through a structured assessment of the literature. A broad and comprehensive literature search was performed to identify studies reporting data on urethral malignancies published since the prior search, covering a time frame between 1 May 2023 and 1 May 2025. Databases searched included Medline, EMBASE and the Cochrane Libraries. A total of 155 unique records were identified, retrieved and screened for relevance. Two new references were included in this 2026 publication. A detailed search strategy is available on the EAU Website: https://uroweb.org/guidelines/primary-urethral-carcinoma/publications-appendices.

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 that accompany each Guidelines recommendation, addresses a number of key elements:

1. the overall quality of the evidence that 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 preferences [5].

Additional methodology information and a list of associations endorsing the EAU Guidelines is available on the EAU Website: https://uroweb.org/eau-guidelines/methodology-policies.

2.2 Review

The PUC Guidelines were 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 and a male/female prevalence of 2.9 to 1 [8]. Likewise, in an updated analysis of the Surveillance, Epidemiology and End Results (SEER) database (2004–2016), the incidence of PUC peaked in the > 75 years age group (7.6/million). The age-standardised rate was 4.3/million in males and 1.5/million in females and was almost negligible in those aged < 55 years (0.2/million) [9]. After matching for tumour and patient characteristics, females present with higher disease stage and exhibited higher cancer-specific mortality (CSM) [10].

3.2 Aetiology

For male PUC, 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 infections (i.e., condylomata associated with human papillomavirus 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 PUC. Mid-urethral sling meshes have not been associated with an increased risk of PUC [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 the SEER database have reported that urothelial carcinoma (UC) of the urethra is the predominant histological type of PUC (54-65%), followed by squamous cell carcinoma (SCC) (16-22%) and AC (10-16%) [8, 27].

A SEER analysis of 2,065 males with PUC (mean age 73 years) found that UC was most common (78%), while SCC (12%) and AC (5%) were significantly less frequent [28]. In females, 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 is very rare and has a poor 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 females - and reported that Mullerian-type tumour is the most frequent unconventional histology of urethral cancer, followed by melanocytic-type histology [31].

4. STAGING AND CLASSIFICATION SYSTEMS

4.1 Tumour, Node, Metastasis classification

In males and females, urethral carcinoma is classified according to the 9th edition of the Tumour, Node, Metastasis (TNM) classification [7] (Table 4.1). 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 (9th 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, or bladder neck (extraprostatic extension)
T4	Tumour invades other adjacent organs (invasion of the bladder)
Urothelial carcinoma of the prostate and prostatic urethra	
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, or 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

Nonurothelial urethral carcinoma is graded by a trinomial system that differentiates between well differentiated (G1), moderately differentiated (G2) and poorly differentiated (G3) tumours. In primary UC, histological subtypes are extremely rare. Table 4.2 lists the various grading systems according to the World Health Organization (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 (ICCR) [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 Recommendation for staging and classification systems

Recommendation	Strength rating
Use the 2025 Tumour, Node, Metastasis classification and 2022 World Health Organization 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 PUC 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 extraurethral mass (52%), bladder outlet obstruction (48%), pelvic pain (33%), urethrocutaneous fistula (10%), abscess formation (5%) or dyspareunia [35].

5.2 Clinical examination

In male patients, physical examination should comprise palpation of the external genitalia for suspicious indurations or masses and digital rectal examination [36]. In female patients, further pelvic examination and palpation of the urethra should be performed. In addition, when necessary, bimanual examination should be performed under general anaesthesia for local clinical staging and to assess whether colorectal or gynaecological malignancies are present.

Bilateral inguinal palpation should be performed to assess the presence of enlarged lymph nodes (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 PUC. Reporting of urinary cytology findings should follow the Paris system [38]. However, the role of urinary cytology in PUC 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, this was reported to be 50% and 77%, respectively [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 male patients 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 specimens should follow the recommendations provided by the ICCR (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 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 exenteration surgery [49].
[^{18}F]fluorodeoxyglucose positron emission tomography (FDG-PET)/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 (approximately 84% of patients) [51-53], which is in contrast to penile cancer where this is the case in approximately 41% of patients [54]. In male patients, 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 female patients, 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 recommendations 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 five-year relative overall survival (OS) rates in patients with urethral carcinoma in Europe are 71% and 54%, respectively [8]. An analysis of data collected between 2000 and 2020 by the SEER database, including 512 patients with non-metastatic PUC, reported CSM rates of 38.2% at five years. In 278 PUC patients with T1–T2, N0 disease and 234 PUC patients with T3–T4, N0–N2 disease, the five-year CSM rates at initial diagnosis was 68.4% and 53.8%, respectively [57]. Based on longer follow-up, an analysis of the SEER database comparing prognostic factors in rare pathological types of PUC (n = 257) and common pathological groups (n = 2,651), reported ten-year OS rates of 42.4% and 31.9%, respectively [58]. Cancer-specific survival (CSS) rates at five and ten years were 68% and 60%, respectively [59]. 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 [58].

6.2 Predictors of survival in primary urethral carcinoma

Previous series reported no substantial difference in five-year OS rates between males versus females [8, 30, 60], whereas in a SEER analysis, female patients showed a higher disease stage and five-year CSM despite the higher use of multimodal therapy [10, 61]. Prognostic factors of worse survival in patients with PUC are:

- advanced age (> 65 years) and Black ethnicity [8, 30, 61, 62]
- unmarried status, as defined by the SEER field description [63]
- higher stage, grade, nodal involvement [52, 64] and metastasis [28]
- increased tumour size and proximal tumour location [28]
- non-urothelial or unconventional histology [8, 28, 62, 64-67]
- presence of concomitant bladder cancer [40]
- scope of surgical treatment and treatment modality [28, 62, 64]
- treatment in non-academic centres [68]
- location of recurrence (solitary or concomitant urethral sites vs. nonurethral sites) [69]

Some limitations must be considered when interpreting these results as the number of patients included in most studies were low [66].

6.3 Summary of evidence for prognosis

Summary of evidence	LE
Prognostic factors for survival in PUC: age, sex, ethnicity, 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 UC 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 (penile urethra and fossa navicularis) 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 [70]. 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 in males with pT1-3N0-2 distal urethral carcinoma that were treated with well-defined, penile-preserving surgery and additional iliac/inguinal lymphadenectomy (LND) for clinically suspected LN disease, even with < 5mm resection margins (median follow-up: 17-37 months) [71]. Similar results for the feasibility of penile-preserving surgery have also been reported [72, 73]. 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 [74].

7.1.1 Summary of evidence and recommendations 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 compared with penile amputation.	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

To provide the highest chance of local cure in females with localised urethral carcinoma, primary radical urethrectomy should include removal of all the periurethral tissue from the bulbocavernosus muscle, bilaterally and distally, with a cylinder of all adjacent soft tissue up to the pubic symphysis and bladder neck. Bladder neck closure and vesicostomy, for example, by using the appendix, for primary distal urethral lesions have been shown to provide satisfactory functional results [37].

Previous series have reported outcomes in females with mainly distal urethral tumours undergoing primary treatment with urethra-sparing surgery, with or without additional radiotherapy (RT), as compared to primary urethrectomy, with the aim of maintaining integrity and function of the lower urinary tract [75, 76]. In longer-term series with a median follow-up of 153-175 months, local recurrence rates in females undergoing partial urethrectomy with intra-operative frozen section analysis were 22-60%, and distal sleeve resection of > 2cm resulted in secondary urinary incontinence in 42% of patients who subsequently required additional reconstructive surgery [75, 76].

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 females with distal urethral carcinoma to prevent local and systemic progression [75].

*7.2.2 **Radiotherapy***

In females, RT was investigated in several older series with a medium follow up of 91-105 months [77]. With a median cumulative dose of 65Gy (range 40-106Gy), the five-year local control rate was 64% and seven-year CSS was 49% [77]. Most local failures (95%) occurred within the first two years after primary treatment [77]. 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 [77]. In one study, the addition of brachytherapy to EBRT reduced the risk of local recurrence by a factor of 4.2 [78]. 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 [77].

*7.2.3 **Summary of evidence and recommendations 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 radiotherapy represent alternatives to primary urethrectomy but are associated with increased risk of tumour recurrence and local toxicity.	3

Recommendations	Strength rating
Offer radical urethrectomy unless specific criteria for organ preservation are met.	Strong
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 PUC consists of definitive surgery plus chemotherapy with additional RT [79]. Multimodal therapy was often underutilised in locally advanced disease (only 16%), notwithstanding promising results [79-82]. In a study, monotherapy was associated with decreased local recurrence-free survival after adjusting for stage, histology, sex and year of treatment ($p = 0.017$). The use of monotherapy has decreased over time [83]. 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 PUC [68].

*7.3.2 **Preoperative systemic treatment***

Retrospective studies reported that cisplatin-based combination chemotherapy regimens can be effective, providing prolonged survival even in LN-positive disease. Moreover, the studies emphasised the critical role of surgery after chemotherapy to achieve long-term survival in patients with locally advanced urethral carcinoma. In an analysis of males with primary UC using the National Cancer Database, neoadjuvant chemotherapy (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 males with primary UC, NAC was reported to exhibit improved OS compared with adjuvant chemotherapy [84].

In a series of 124 patients, 39 (31%) were treated with perioperative platinum-based chemotherapy for advanced PUC (12 received NAC; 6 received neoadjuvant chemoradiotherapy; and 21 adjuvant chemotherapy). Patients who received NAC or chemoradiotherapy for locally advanced PUC (> cT3 and/or cN+) appeared to demonstrate improved survival compared to those who underwent upfront surgery with or without adjuvant chemotherapy [85]. Another retrospective series, including 44 patients with advanced PUC, 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 was 32 months [51].

Recent advances in the management of MIBC, including adjuvant immunotherapy and perioperative chemo-immunotherapy, should be considered for the treatment of patients with locally advanced PUC such that if UC is the predominant histology, the EAU MIBC Guidelines [2] can be followed.

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 the potential for genital preservation [86-90]. The largest 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 five-year OS and disease-specific survival was 52% and 68%, respectively. Salvage surgery, initiated only in non-responders or in cases of local failure, was not reported to be associated with improved survival [86].

A large retrospective cohort study in patients with locally advanced urethral carcinoma treated with adjuvant RT and surgery versus surgery alone demonstrated that the addition of RT improved OS [91].

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 [69].

7.3.5 Treatment of regional lymph nodes

Nodal control in urethral carcinoma can be achieved either by regional LND [36], RT [77] 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 has been 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 recommendations 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 UC 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
Determine perioperative treatment according to histology in locally advanced urethral carcinoma treated with curative intent.	Weak
Follow the European Association of Urology Guidelines on Muscle-invasive and Metastatic Bladder Cancer for the use of perioperative systemic therapy in patients with locally advanced urethral urothelial carcinoma.	Weak
Offer the combination of curative radiotherapy (RT) with radiosensitising chemotherapy for definitive treatment and genital preservation in locally advanced squamous cell carcinoma (SCC) of the urethra.	Weak
Offer salvage surgery or RT to patients with urethral recurrence after primary treatment.	Weak
Offer inguinal lymph node (LN) dissection to patients with LN-positive urethral SCC when all involved inguinal LNs are macroscopically resectable.	Weak

7.4 Treatment of urothelial carcinoma of the prostate

Local conservative treatment with extensive TUR and subsequent bacillus Calmette-Guérin (BCG) instillation is effective in patients with Ta or Tis prostatic urethral carcinoma [92]. A systematic review reported that patients treated with transurethral resection of the prostate (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 [93]. 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 [94, 95]. In 24 patients with prostatic stromal invasion treated with radical cystoprostatectomy, an LN mapping study found that 12 patients had positive LNs, with an increased proportion located above the iliac bifurcation [96].

7.4.1 Summary of evidence and recommendations for the treatment of urothelial carcinoma of the prostate

Summary of evidence	LE
Patients undergoing TURP for prostatic UC prior to BCG treatment show superior complete response rates compared to those who do not.	3

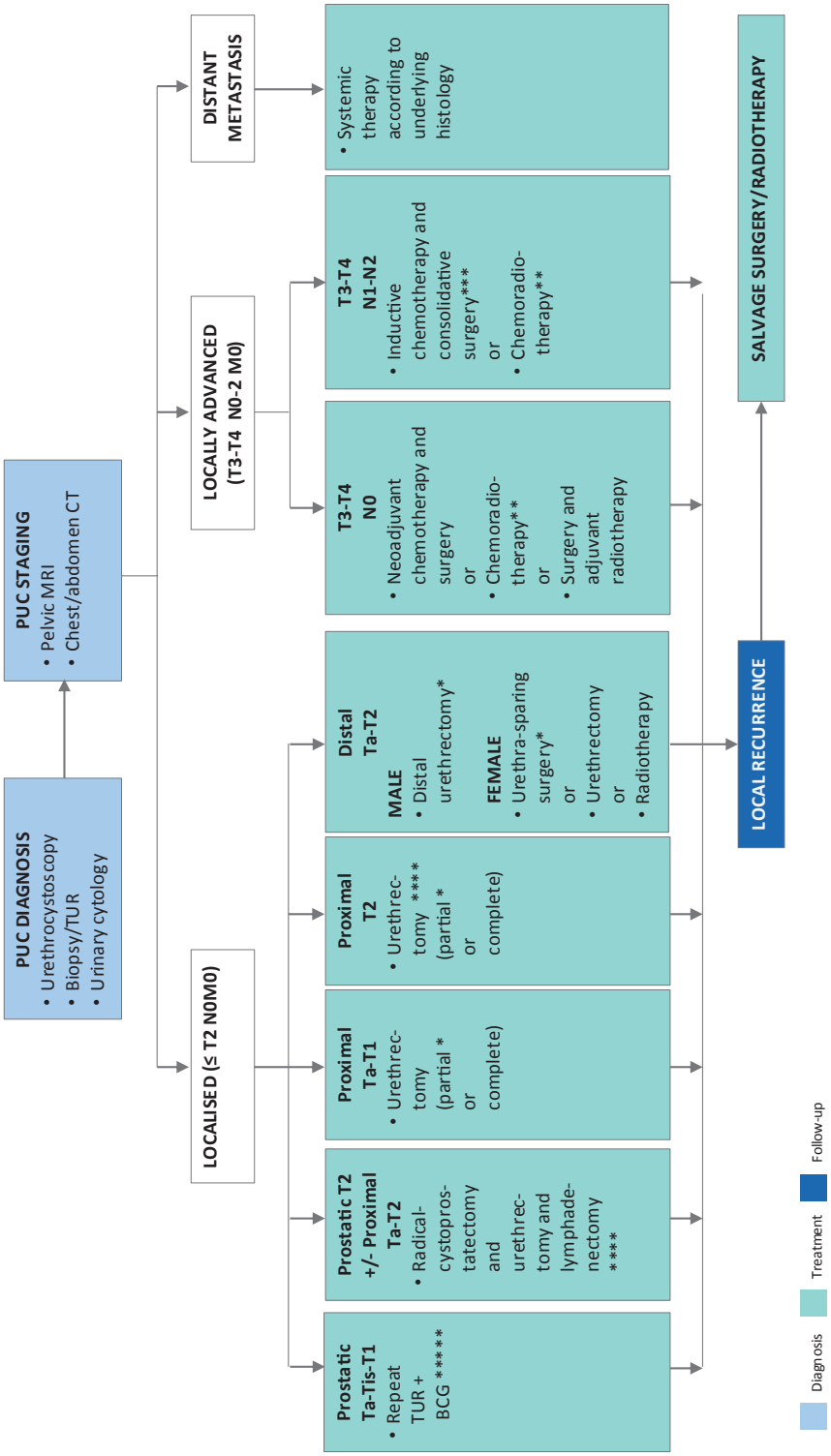
Recommendations	Strength rating
Offer a urethra-sparing approach with transurethral resection and bacillus Calmette-Guérin (BCG) to patients with non-invasive urethral carcinoma or carcinoma *in situ* of the prostatic urethra and prostatic ducts.	Strong
In patients not responding to BCG, or in patients with ductal or stromal involvement, perform a cystoprostatectomy with extended pelvic lymphadenectomy.	Weak

7.5 Metastatic disease

An analysis of the SEER database reported that patients with M1 disease who underwent primary site surgery did not exhibit any survival benefit [60]. Systemic therapy in metastatic disease should be selected based on the histology of the tumour. The EAU MIBC Guidelines can be followed if UC is the predominant histology [2]. Although patients with urethral carcinoma have been included in large clinical trials on immunotherapy, no subgroup analyses of response rates have been reported to date [97].

In addition, there is an urgent clinical need to better address the role of local palliative treatment strategies in PUC, including surgery, which has been shown to positively impact QoL aspects in select patients with advanced genital cancers [98].

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 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 PUC, 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

The clinical literature shows clear gaps related to the diagnosis, management and follow-up of patients with PUC. 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 European Reference Network for rare and complex urogenital diseases and conditions (eUROGEN) initiative.

The Panel identified the following topics 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 PUC
- The role of MRI in the local assessment of response to therapy.

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10. CONFLICT OF INTEREST

All members of the MIBC 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 available on the EAU Website: http://www.uroweb.org/guidelines/primary-urethral-carcinoma/panel.

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Disclosures: The EAU Guidelines Office certifies that all conflicts of interest, including specific financial interests and relationships and affiliations relevant to the subject matter or materials discussed in the manuscript (e.g., employment/affiliation, grants or funding, consultancies, honoraria, stock ownership or options, expert testimony, royalties, or patents filed, received or pending), are the following:

Y. Neuzillet reported receiving company speaker honoraria or consultation fees from AstraZeneca, Bristol-Myers Squibb, Merck, Astellas and MSD. A.G. van der Heijden reported receiving company speaker honoraria fees from Merck Sharp & Dohme B.V.; and serving as a company consultant to Astellas Pharma International B.V., Johnson & Johnson Innovative Medicine, Merck Sharp & Dohme B.V. and Pfizer B.V. A. Carrión reported receiving company speaker honoraria, travel or consultation fees from Johnson & Johnson, Gebro, BMS and BC Platform; serving as a company consultant to BC Platforms; and participation in clinical trials by Janssen Research & Development, LLC. R. Cathomas reported receiving company speaker honoraria or consultation fees from Astellas, Astra Zeneca, Bayer, BMS, Johnson & Johnson, MSD, Pfizer, Roche, Merck Serono and Ipsen. K. Dimitropoulos reported receiving company speaker honoraria fees from Astellas and Ipsen. J.A. Efstathiou reported receiving company speaker honoraria or consultation fees from Astellas; and serving as a company consultant for Boston Scientific and Blue Eagle Diagnostics. E.M. Compérat reported serving as a company consultant to Daiitchi, Johnson and Astra. B. Kiss reported serving as a company consultant on the advisory board of Pfizer and Astra Zeneca. A. Lorch reported receiving company speaker honoraria or consultation fees from Astellas, Astra Zeneca, Bayer, BMS, Esai, Ipsen, Janssen, Merck, MSD, Novartis, Pfizer and Roche; receiving travel grants from Ipsen, Janssen and Bayer; participation in clinical trials as a principal investigator; and contributing as an author to the Onkopedia guidelines. P. Mariappan reported receiving company speaker honoraria fees from Bristol Myers Squibb, Janssen Cilag Ltd., Medac Pharma and Photocure; serving on the core committee of the International Bladder Cancer Group; receiving grants or research support from Nucleix; and participation in clinical trials by Nucleix. R.P. Meijer reported receiving grants or research support from Astellas Pharma International B.V., Gilead Sciences, Janssen Vaccines & Prevention B.V. and Merck Sharp & Dohme B.V. L.S. Mertens reported receiving company speaker honoraria fees from Johnson & Johnson Medical B.V. and MSD (paid to hospital). M.I. Milowsky reported receiving grants or research support from Merck, Bristol-Myers Squibb, Alliance for Clinical Trials in Oncology, ALX Oncology, Novartis, Acrivon Therapeutics, PCCTC, OncoC4, Flare Therapeutics, Loxo/Lilly, Astellas Pharma, Pfizer, Amgen, Roche and G1 Therapeutics; being a stock shareholder in Pfizer and Gilead Sciences; presenting continuing medical education at Prime Education,

Research to Practice and OncLive/MJH Life Sciences; and acting as uncompensated advisor to G1 Therapeutics and Loxo/Lilly. M. Rink reported receiving company speaker honoraria fees from Johnson & Johnson, Astellas, AstraZeneca, Bayer, BMS, EUSA, Eisai, Ipsen, Medac, Merck Healthcare, MSD, Olympus, Pfizer, Photocure and Roche; serving as a company consultant to Olympus, Johnson & Johnson, BMS, Bayer, Boston Scientific, Eisai, Ipsen, Merck Healthcare, MSD, Pfizer and Roche; and participation in clinical trials by Aveo Pharmaceuticals, BMS, Calithera Bioscience, Excelixis, Ipsen, MSD, Merck Healthcare, Novartis, Pfizer and Roche. J. Shaw reported being an unremunerated trustee of Fight Bladder Cancer, a United Kingdom charity organisation. A. Martini reported receiving company speaker honoraria or consultation fees from Ferring Pharma and UroGen Pharma; and being a stock shareholder in a non-public company. H.M. Bruins, R. Fietkau, V. Panebianco, G.N. Thalmann, S. Sæbjørnsen and M. Kailavasan have nothing to declare.

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