Guidelines on Primary Urethral Carcinoma

G. Gakis, J.A. Witjes, E. Compérat, N.C. Cowan, M. De Santis,
T. Lebret, M.J. Ribal, A. Sherif, A.G. van der Heijden

European
Association
of Urology

TABLE OF CONTENTS PAGE

1. INTRODUCTION

1.1 Aims and scope

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

1.2 Panel composition

The EAU Guidelines Panel on Muscle-invasive and Metastatic Bladder Cancer is responsible for this publication. This is an international multidisciplinary group of clinicians, including a pathologist, an oncologist and a radiologist. Members of this panel have been selected based on their expertise to represent the professionals treating patients suspected of harbouring urethral carcinoma.

All experts involved in the production of this document have submitted potential conflict of interest statements.

1.3 Publication history and summary of changes

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

1.3.1 Summary of changes

The literature for the complete document has been assessed and updated, whenever relevant.
Key changes for the 2015 publication:

- Evaluation of recent data on prognostic factors on oncologic outcomes in primary UC;
- Evaluation of recent data on the degree of concordance between clinical and pathologic staging;
- Evaluation of recent data on distal urethrectomy in men;
- Evaluation of recent data on the prognostic effect of multimodal treatment in advanced primary UC.

Conclusions and recommendations have been rephrased and added throughout the document, not resulting in a change in the level of evidence (LE) or grade of recommendation (GR). These changes can be found in the following sections:

6.2 Predictors of survival in primary urethral carcinoma

Conclusion	LE
Risk factors for survival in primary UC are: age, race, tumour stage and grade, nodal stage, presence of distant metastasis, histological type, tumour size, tumour location, concomitant bladder cancer and type and modality of treatment.	3

7.1 Treatment of localised primary urethral carcinoma in males

Recommendation	LE	GR
In localised anterior urethral tumours, distal urethrectomy presents an alternative to achieve negative surgical margins and should be offered as an alternative to penile amputation.	3	B

*7.2.2 **Radiotherapy***

Recommendations	LE	GR
In women, local radiotherapy is an alternative to urethral surgery for localised urethral tumours but local toxicity needs to be considered.	3	C

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

Conclusions	LE
In locally advanced UC, cisplatin-based chemotherapy with curative intent prior to surgery improves survival compared to chemotherapy alone or surgery followed by chemotherapy.	4
In locally advanced squamous cell carcinoma (SCC) of the urethra, the prognostic role and timing of surgery after completion of chemoradiotherapy is unclear.	4

Recommendations	LE	GR
Chemotherapeutic regimens with curative intent prior to surgery should be cisplatinum-based.	4	C
In locally advanced SCC of the urethra, combination of curative radiotherapy with radiosensitising chemotherapy is an option for genital preservation.	4	C

SCC = squamous cell carcinoma; UC = urethral carcinoma.

2. METHODS

2.1 Literature identification

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

In this 2015 EAU Guidelines compilation, all standard information on levels of evidence (LE) and grading of recommendations (GR) has been taken out of the individual guidelines topics for the sake of brevity. This information is included in the introductory section of this print.

2.2 Review

This document was subjected to double-blind peer review prior to publication.

3. EPIDEMIOLOGY, AETIOLOGY AND PATHOLOGY

3.1 Epidemiology

Primary UC is considered a rare cancer, accounting for < 1% of all malignancies [4] (ICD-O3 topography code: C68.0 [5]).

In early 2008, the prevalence of UC in the 27 EU countries was 4,292 cases with an estimated annual incidence of 655 new cases [6]. The age-standardised ratio was 1.1 per million inhabitants (1.6/million in men and 0.6/million in women; with a male to female ratio of 2.9) [6]. There were differences between European regions; potentially caused by registration or classification [6]. Likewise, in an analysis of the Surveillance, Epidemiology and End Results (SEER) database, the incidence of primary UC peaked in the ≥ 75 years age group (7.6/million). The age-standardised rate was 4.3/million in men and 1.5/million in women, and was almost negligible in those aged < 55 years (0.2/million) [7].

3.2 Aetiology

For male primary UC, various predisposing factors have been reported, including urethral strictures [8, 9], chronic irritation after intermittent catheterisation/urethroplasty [10-12], external beam irradiation therapy [13], radioactive seed implantation [14], and chronic urethral inflammation/urethritis following sexually transmitted diseases (i.e. condylomata associated with human papilloma virus 16) [15, 16]. In female UC, urethral diverticula [17-19] and recurrent urinary tract infections [20] have been associated with primary urethral carcinoma. Clear cell adenocarcinoma may also have a congenital origin [21, 22].

3.3 Histopathology

Both the Surveillance of Rare Cancers in Europe (RARECARE) project and SEER database have reported that urothelial carcinoma of the urethra is the predominant histological type of primary urethral cancer (54-65%), followed by squamous cell carcinoma (SCC; 16-22%) and adenocarcinoma (AC; 10-16%) [6, 7]. A recent SEER

analysis of 2,065 men with primary urethral cancer (mean age: 73 years) found that urothelial carcinoma (78%) was most common, and SCC (12%) and AC (5%) were significantly less frequent [23]. In women, a recent report of the Dutch National Cancer Registry on primary urethral cancer reported that urothelial carcinoma occurred in 45% of cases, followed by AC in 29%, SCC in 19%, and other histological entities in 6% [24].

4. STAGING AND CLASSIFICATION SYSTEMS

4.1 Tumor, Node, Metastasis (TNM) staging system

In men and women, UC is classified according to the 7th edition of the TNM classification [5] (Table 4.1). It should be noted that there is a separate TNM staging system for prostatic UC [5]. Of note, for cancers occurring in urethral diverticulum stage, T2 is not applicable as urethral diverticula are lacking periurethral muscle [25].

Table 4.1: TNM classification (7th edition) for UC [5]. Primary tumour stage is separated into UC and UC of the prostate

T - Primary tumour (men and women)	
Tx	Primary tumour cannot be assessed
Tis	Carcinoma *in situ*
T0	No evidence of primary tumour
Ta	Non-invasive papillary carcinoma
T1	Tumour invades subepithelial connective tissue
T2	Tumour invades any of the following structures: corpus spongiosum, prostate, peri-urethral muscle
T3	Tumour invades any of the following structures: corpus cavernosum, invasion beyond prostatic capsule, anterior vaginal wall, bladder neck
T4	Tumour invades other adjacent organs
Primary tumour in prostatic urethra	
Tx	Primary tumour cannot be assessed
Tis pu	Carcinoma *in situ* in the prostatic urethra
Tis pd	Carcinoma *in situ* in the prostatic ducts
T0	No evidence of primary tumour
T1	Tumour invades subepithelial connective tissue (only in case of concomitant prostatic urethral involvement)
T2	Tumour invades any of the following structures: corpus spongiosum, prostatic stroma, periurethral muscle
T3	Tumour invades any of the following structures: corpus cavernosum, beyond prostatic capsule, bladder neck
T4	Tumour invades other adjacent organs
N - Regional lymph nodes	
Nx	Regional lymph nodes cannot be assessed
N0	No regional lymph node metastases
N1	Metastasis in a single lymph node ≤ 2 cm in greatest dimension
N2	Metastasis in a single lymph node > 2 cm in greatest dimension or in multiple nodes
M - Distant metastasis	
Mx	Distant metastasis cannot be assessed
M0	No distant metastasis
M1	Distant metastasis

4.2 Tumour grade

The former World Health Organization (WHO) grading system of 1973 which differentiated urothelial carcinomas into three different grades (G1-G3) has been replaced by the grading system of 2004 that differentiates urothelial UC into papillary urothelial neoplasm of low malignant potential (PUNLMP), low grade and high grade. Non-urothelial UC is graded by a trinomial system that differentiates between well-differentiated (G1), moderately differentiated (G2), and poorly differentiated tumours (G3). Table 4.2 lists the different grading systems according to the WHO 1973 and 2004 systems [26].

Table 4.2: Histopathological grading of urothelial and non-urothelial primary UC [26]

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

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

Recommendation	LE	GR
Pathological staging and grading of primary UC should follow the 2009 TNM classification and WHO 2004 grading system.	3	B

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

5. DIAGNOSTIC EVALUATION AND STAGING

5.1 History

When becoming clinically apparent, most patients (45-57%) with primary UC present with symptoms associated with locally advanced disease (T3/T4) [25, 27]. 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 [27].

5.2 Clinical examination

In men, physical examination should comprise palpation of the external genitalia for suspicious indurations or masses and digital rectal examination [28]. In women, further pelvic examination with careful inspection and palpation of the urethra should be performed, especially in those with primary onset of irritative or obstructive voiding. In addition, bimanual examination, when necessary under general anaesthesia, should be performed for local clinical staging and to exclude the presence of colorectal or gynaecological malignancies. Bilateral inguinal palpation should be conducted to assess the presence of enlarged lymph nodes, describing location, size and mobility [29].

5.3 Urinary cytology

The role of urinary cytology in primary UC is limited, and its sensitivity ranges between 55% and 59% [30]. Detection rate depends on the underlying histological entity. In male patients, the sensitivity for urothelial carcinoma 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 urothelial carcinoma.

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 [28]. To enable accurate pathological assessment of surgical margins, biopsy sites (proximal/distal end) should be marked and sent together with clinical information to the pathologist.

Careful cystoscopic examination is necessary to exclude the presence of concomitant bladder tumours [3, 31]. A cold-cup biopsy enables accurate tissue retrieval for histological analysis and avoids artificial tissue damage. In patients with larger lesions, transurethral resection (optionally in men under penile blood arrest using a tourniquet) can be performed for histological diagnosis. In patients with suspected urothelial carcinoma of the prostatic urethra or ducts, resectoscope loop biopsy of the prostatic urethra (at 5 and 7 o'clock positions from the bladder neck and distally around the area of the verumontanum) can contribute to an improved detection rate [32].

5.5 Radiological imaging

Radiological imaging of urethral cancer aims to assess local tumour extent and to detect lymphatic and distant metastatic spread. For local staging, there is increasing evidence that magnetic resonance imaging (MRI) is an accurate tool for monitoring tumour response to neoadjuvant chemoradiotherapy and evaluating the extent of local disease prior to exenterative surgery [33]. Imaging for regional lymph node metastases should concentrate on inguinal and pelvic lymph nodes, using either MRI or CT. Distant staging should concentrate on chest and liver, with CT of the thorax and abdomen in all patients with invasive disease (≥ cT1N0M0 [33-37]. If imaging of the remainder of the urothelium is required, then CT should include CT urography with an excretory phase [38].

5.6 Regional lymph nodes

Enlarged lymph nodes in urethral cancer often represent metastatic disease [39, 40]. In men, lymphatics from the anterior urethra drain into the superficial- and deep inguinal lymph nodes and subsequently to the pelvic (external, obturator and internal iliac) lymph nodes. Conversely, lymphatic vessels of the posterior urethra drain into the pelvic lymph nodes. In women, the lymph of the proximal third drains into the pelvic lymph node chains, whereas the distal two-thirds initially drain into the superficial- and deep inguinal nodes [41, 42].

Nodal control in urethral cancer can be achieved either by regional lymph node dissection [28], radiotherapy [43] or chemotherapy [39]. Currently, there is still no clear evidence to support prophylactic bilateral inguinal and/or pelvic lymphadenectomy in all patients with urethral cancer. However, in patients with clinically enlarged inguinal/pelvic lymph nodes or invasive tumours, regional lymphadenectomy should be considered for initial treatment because cure might still be achievable with limited disease [28].

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

Recommendations	LE	GR
Diagnosis includes urethrocystoscopy with biopsy and urinary cytology.	3	B
CT of the thorax and abdomen should be used to assess distant metastases.	3	B
Pelvic MRI is the preferred method to assess local extent of urethral tumour.	3	B

CT = computed tomography; MRI = magnetic resonance imaging.

6. PROGNOSIS

6.1 Long-term survival after primary urethral carcinoma

According to the RARECARE project, the mean 1- and 5-year overall survival in patients with UC in Europe is 71% and 54%, respectively [6]. With longer follow-up, a SEER analysis of 1,615 cases reported median 5- and 10-year overall survival rates of 46% and 29%, respectively. Cancer-specific survival at 5 and 10 years was 68% and 60%, respectively [7].

6.2 Predictors of survival in primary urethral carcinoma

In Europe, mean 5-year overall survival does not substantially differ between the sexes [6]. Predictors of decreased survival in patients with primary UC are:

- advanced age (≥ 65 years) and black race [6, 44];
- stage, grade, nodal involvement [40] and metastasis [23];
- tumour size and proximal tumour location [23];
- extent of surgical treatment and treatment modality [23, 44];
- underlying histology [6, 24, 44];
- presence of concomitant bladder cancer [31].

Some limitations have to be taken into account in the interpretation of these results. In the Dutch study, the numbers were low (n = 91) [25]. In the large SEER database (n = 2,046), therapy is not well specified in relation to survival [24]. Finally, in contrast to the RARECARE project [6], the opposite findings were reported in the SEER database in relation to the role of histology on survival in male patients [44].

Conclusion	LE
Risk factors for survival in primary UC are: age, race, tumour stage and grade, nodal stage, presence of distant metastasis, histological type, tumour size, tumour location, concomitant bladder cancer and type and modality of treatment.	3

7. DISEASE MANAGEMENT

7.1 Treatment of localised primary urethral carcinoma in males

Previously, treatment of male anterior urethral cancer has followed the procedure for penile cancer, with aggressive surgical excision of the primary lesion with a wide safety margin [28]. Distal urethral tumours exhibit significantly improved survival rates compared with proximal tumours [45]. Therefore, optimising treatment of distal urethral cancer has become the focus of clinicians to improve functional outcome and quality of life, while preserving oncological safety. A retrospective series found no evidence of local recurrence, even with < 5 mm resection margins (median follow-up: 17-37 months), in men with pT1-3N0-2 anterior UC treated with well-defined penis-preserving surgery and additional iliac/inguinal lymphadenectomy for clinically suspected lymph node disease [46]. This suggests that prognosis is mainly determined by nodal stage. Similar results for the feasibility of penile-preserving surgery have been also reported in a recent series [47].

Recommendation	LE	GR
In localised anterior urethral tumours, distal urethrectomy presents an alternative to achieve negative surgical margins and should be offered as an alternative to penile amputation.	3	B

7.2 Treatment of localised urethral carcinoma in females

*7.2.1 **Urethrectomy and urethra-sparing surgery***

In women with localised urethral cancer, to provide the highest chance of local cure, primary radical urethrectomy should remove all the periurethral tissue from the bulbocavernosus muscle bilaterally and distally, with a cylinder of all adjacent soft tissue up to the pubic symphysis and bladder neck. Bladder neck closure and via an appendico-vesicostomy for primary anterior urethral lesions has been shown to provide satisfactory functional results in women [28].

Recent series have reported outcomes in women with mainly anterior urethral cancer undergoing primary treatment with urethra-sparing surgery or radiotherapy, compared to primary urethrectomy, with the aim of maintaining integrity and function of the lower urinary tract [48-50]. In long-term series with a median follow-up of 153-175 months, local recurrence rates in women undergoing partial urethrectomy with intraoperative frozen section analysis were 22-60%, and distal sleeve resection of > 2 cm resulted in secondary urinary incontinence in 42% of patients who required additional reconstructive surgery [48, 49]. Ablative surgical techniques, i.e., transurethral resection (TUR) or laser, used for small distal urethral cancer, have also resulted in a considerable local failure rate of 16%, with a cancer-specific survival rate of 50%. This emphasises the critical role of local tumour control in women with distal urethral cancer to prevent local and systemic progression [48].

*7.2.2 **Radiotherapy***

In women, radiotherapy was investigated in several older long-term series with a medium follow-up of 91-105 months [43, 46]. With a median cumulative dose of 65 Gy (range: 40-106 Gy), the 5-year local control rate was 64% and 7-year cancer-specific survival was 49% [43]. Most local failures (95%) occurred within the first two years after primary treatment [46]. The extent of urethral tumour involvement was found to be the only parameter independently associated with local tumour control but the type of radiotherapy (external beam radiotherapy vs. interstitial brachytherapy) was not [43]. In one study, the addition of brachytherapy to external beam radiotherapy reduced the risk of local recurrence by a factor of 4.2 [51]. Of note, pelvic toxicity in those achieving local control was considerable (49%), including urethral stenosis, fistula, necrosis, and cystitis and/or haemorrhage, with 30% of the reported complications graded as severe [43].

Recommendations	LE	GR
In women with anterior urethral tumours, urethra-sparing surgery is an alternative to primary urethrectomy if negative surgical margins can be achieved intraoperatively.	3	B
In women, local radiotherapy is an alternative to urethral surgery for localised urethral tumours but local toxicity needs to be considered.	3	C

7.3 Multimodal treatment in advanced urethral carcinoma in both genders

*7.3.1 **Preoperative platinum-based chemotherapy***

Recent retrospective studies have reported that modern platinum-based polychemotherapeutic regimens are effective in advanced primary urethral cancer, providing prolonged survival even in lymph-node-positive disease. Moreover, they have emphasised the critical role of surgery after chemotherapy for achieving long-term survival in patients with locally advanced urethral cancer.

In a series of 39 patients treated with perioperative platinum-based chemotherapy for advanced primary UC, preoperative chemotherapy was found to be associated with improved progression-free and overall survival compared to surgery followed by adjuvant chemotherapy [52]. Another series reported outcomes in 44 patients with advanced primary urethral cancer treated with specific cisplatin-based polychemotherapeutic regimens according to the underlying histology. The overall response rate for the various regimens was 72% and the median overall survival 32 months. Patients who underwent surgery after chemotherapy had significantly improved overall survival compared with those who were managed with chemotherapy alone [39].

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

The clinical feasibility of preoperative local radiotherapy with concurrent radiosensitising chemotherapy as an alternative to surgery in locally advanced SCC has been reported in several recent series. This approach offers a potential for genital preservation [52-57]. The largest and recently updated series reported outcomes in 25 patients with primary locally advanced SCC of the urethra treated with two cycles of 5-fluorouracil and mitomycin C with concurrent external beam radiotherapy. A complete response to primary chemoradiotherapy was observed in ~80%. The 5-year overall- and disease-specific survival was 52% and 68%, respectively. In this updated series, salvage surgery initiated only in non-responders or in case of local failure was not reported to be associated with improved survival [53].

Conclusions	LE
In locally advanced UC, cisplatin-based chemotherapy with curative intent prior to surgery improves survival compared to chemotherapy alone or surgery followed by chemotherapy.	4
In locally advanced SCC of the urethra, the prognostic role and timing of surgery after completion of chemoradiotherapy is unclear.	4

Recommendations	LE	GR
Patients with locally advanced UC should be discussed within a multidisciplinary team of urologists, radio-oncologists and oncologists.	4	A
Chemotherapeutic regimens with curative intent prior to surgery should be cisplatinum-based.	4	C
In locally advanced SCC of the urethra, combination of curative radiotherapy with radiosensitising chemotherapy is an option for genital preservation.	4	C

SCC = squamous cell carcinoma; UC = urothelial carcinoma.

7.4 Treatment of urothelial carcinoma of the prostate

Local conservative treatment with extensive TUR and subsequent Bacille-Calmette-Guérin (BCG) instillation is effective in patients with Ta or Tis prostatic UC [58, 59]. Likewise, patients undergoing TUR of the prostate prior to BCG experience improved complete response rates compared with those who do not (95% vs. 66%) [60]. Risk of understaging local extension of prostatic urethral cancer at TUR is increased, especially in patients with ductal or stromal involvement [61]. In smaller series, response rates to BCG in patients with prostatic duct involvement have been reported to vary between 57 and 75% [58, 62]. 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 [63, 64]. In 24 patients with prostatic stromal invasion treated with radical cystoprostatectomy, a lymph node mapping study found that 12 patients had positive lymph nodes, with an increased proportion located above the iliac bifurcation [65].

Recommendations	LE	GR
Patients with non-invasive UC or carcinoma *in situ* of the prostatic urethra and prostatic ducts can be treated with a urethra-sparing approach with TUR and BCG.	3	C
In patients with non-invasive UC or carcinoma *in situ*, prior TUR of the prostate should be performed to improve response to BCG.	3	C
Cystoprostatectomy with extended pelvic lymphadenectomy should be reserved for patients not responding to BCG or as primary treatment option in patients with extensive ductal or stromal involvement.	3	C

BCG = Bacille-Calmette-Guérin; TUR = transurethral resection; UC = urothelial carcinoma.

8. FOLLOW-UP

COMMENTARY: Given the low incidence of primary urethral cancer, defined follow-up has not been investigated systematically so far. Therefore, it seems reasonable to tailor surveillance regimens according to the patients' individual risk factors (Chapter 6.2). In patients undergoing urethra-sparing surgery, it seems prudent to advocate a more extensive follow-up with urinary cytology, urethrocytoscopy and cross-sectional imaging despite the lack of specific data.

9. REFERENCES

1. Boorjian SA, Kim SP, Weight CJ, et al. Risk factors and outcomes of urethral recurrence following radical cystectomy. Eur Urol 2011 Dec;60(6):1266-72. http://www.ncbi.nlm.nih.gov/pubmed/21871713
2. Witjes JA, Compérat E, Cowan NC, et al; members of the EAU Guidelines Panel on Muscle-invasive and Metastatic Bladder Cancer. EAU Guidelines on Muscle-invasive and Metastatic Bladder Cancer. Edn. presented at the EAU Annual Congress Madrid 2015. ISBN 978-90-79754-80-9. Arnhem, The Netherlands. http://www.uroweb.org/guidelines/online-guidelines/
3. Gakis G, Witjes JA, Compérat E, et al. EAU guidelines on primary urethral carcinoma. Eur Urol 2013 Nov;64(5):823-30. http://www.ncbi.nlm.nih.gov/pubmed/23582479
4. Gatta G, van der Zwan JM, Casali PG, et al; The RARECARE working group. Rare cancers are not so rare: The rare cancer burden in Europe. Eur J Cancer 2011; Nov;47(17):2493-511. http://www.ncbi.nlm.nih.gov/pubmed/22033323
5. Sobin LH, Gospodariwicz M, Wittekind C (eds). TNM classification of malignant tumors. UICC International Union Against Cancer. 7th edn. Wiley-Blackwell, 2009 Dec; pp. 266-9. http://www.uicc.org/tnm/
6. Visser O, Adolfsson J, Rossi S, et al; The RARECARE working group. Incidence and survival of rare urogenital cancers in Europe. Eur J Cancer 2012 Mar;48(4):456-64; http://www.ncbi.nlm.nih.gov/pubmed/22119351
7. Swartz MA, Porter PM, Lin DW, et al. Incidence of primary urethral carcinoma in the United States. Urology 2006 Dec;68(6):1164-8. http://www.ncbi.nlm.nih.gov/pubmed/17141838
8. Medina Pérez M, Valero Puerta J, Sánchez González M, et al. (Squamous carcinoma of the male urethra, its presentation as a scrotal abscess.) Arch Esp Urol 1999 Sep;52(7):792-4. [Article in Spanish] http://www.ncbi.nlm.nih.gov/pubmed/10540772
9. Van de Voorde W, Meertens B, Baert L, et al. Urethral squamous cell carcinoma associated with urethral stricture and urethroplasty. Eur J Surg Oncol 1994 Aug;20(4):478-83. http://www.ncbi.nlm.nih.gov/pubmed/8076714
10. Colapinto V, Evans DH. Primary carcinoma of the male urethra developing after urethroplasty for stricture. J Urol 1977 Oct;118:581-4. http://www.ncbi.nlm.nih.gov/pubmed/916053

11. Mohanty NK, Jolly BB, Saxena S, et al. Squamous cell carcinoma of perineal urethrostomy. Urol Int 1995;55(2):118-9. http://www.ncbi.nlm.nih.gov/pubmed/8533195
12. Sawczuk I, Acosta R, Grant D,et al. Post urethroplasty squamous cell carcinoma. N Y State J Med 1986 May;86(5):261-3. [No abstract available] http://www.ncbi.nlm.nih.gov/pubmed/3459083
13. Mohan H, Bal A, Punia RP, et al. Squamous cell carcinoma of the prostate. Int J Urol 2003 Feb;10:114-6. http://www.ncbi.nlm.nih.gov/pubmed/12588611
14. Arva NC, Das K. Diagnostic dilemmas of squamous differentiation in prostate carcinoma case report and review of the literature. Diagn Pathol 2011 May;6:46 http://www.ncbi.nlm.nih.gov/pubmed/21627811
15. Cupp MR, Malek RS, Goellner JR, et al. Detection of human papillomavirus DNA in primary squamous cell carcinoma of the male urethra. Urology 1996 Oct;48(4):551-5. http://www.ncbi.nlm.nih.gov/pubmed/8886059
16. Wiener JS, Liu ET, Walther PJ. Oncogenic human papillomavirus type 16 is associated with squamous cell cancer of the male urethra. Cancer Res 1992 Sep;52(18):5018-23. http://www.ncbi.nlm.nih.gov/pubmed/1325290
17. Ahmed K, Dasgupta R, Vats A, et al. Urethral diverticular carcinoma: an overview of current trends in diagnosis and management. Int Urol Nephrol 2010 Jun;42(2):331-41. http://www.ncbi.nlm.nih.gov/pubmed/19649767
18. Chung DE, Purohit RS, Girshman J, et al. Urethral diverticula in women: discrepancies between magnetic resonance imaging and surgical findings. J Urol 2010 Jun;183(6):2265-9. http://www.ncbi.nlm.nih.gov/pubmed/20400161
19. Thomas AA, Rackley RR, Lee U, et al. Urethral diverticula in 90 female patients: a study with emphasis on neoplastic alterations. J Urol 2008 Dec;180(6):2463-7. http://www.ncbi.nlm.nih.gov/pubmed/18930487
20. Libby B, Chao D, Schneider BF. Non-surgical treatment of primary female urethral cancer. Rare Tumors 2010 Sep 30;2(3):e55. http://www.ncbi.nlm.nih.gov/pubmed/21139970
21. Gandhi JS, Khurana A, Tewari A, et al. Clear cell adenocarcinoma of the male urethral tract. Indian J Pathol Microbiol 2012 Apr-Jun;55(2):245-7. http://www.ncbi.nlm.nih.gov/pubmed/22771656
22. Mehra R, Vats P, Kalyana-Sundaram S, et al. Primary urethral clear-cell adenocarcinoma: comprehensive analysis by surgical pathology, cytopathology, and next-generation sequencing. Am J Pathol 2014 Mar;184(3):584-91. http://www.ncbi.nlm.nih.gov/pubmed/24389164
23. Rabbani F. Prognostic factors in male urethral cancer. Cancer 2011 June 117(1):2426-34. http://www.ncbi.nlm.nih.gov/pubmed/24048790
24. Derksen JW, Visser O, de la Rivière GB, et al. Primary urethral carcinoma in females: an epidemiologic study on demographical factors, histological types, tumour stage and survival. World J Urol 2013 Feb;31(1):147-53.. http://www.ncbi.nlm.nih.gov/pubmed/22614443
25. Golijanin D, Yossepowitch O, Beck SD, et al. Carcinoma in a bladder diverticulum: presentation and treatment outcome. J Urol 2003 Nov;170(5):1761-4. http://www.ncbi.nlm.nih.gov/pubmed/14532771
26. WHO Classification of Tumours: Pathology and Genetics of Tumours of the Urinary System and Male Genital Organs (IARC WHO Classification of Tumours) eds. E.J. Eble J, Sesterhenn I, Sauter G. 2004, Lyon: IARC Press. http://www.iarc.fr/en/publications/pdfs-online/pat-gen/bb7/BB7.pdf
27. Gheiler EL, Tefilli MV, Tiguert R, et al. Management of primary urethral cancer. Urology 1998 Sep;52(3):487-93. http://www.ncbi.nlm.nih.gov/pubmed/9730466
28. Karnes RJ, Breau RH, Lightner DJ. Surgery for urethral cancer. Urol Clin North Am 2010 Aug;37(3):445-57. http://www.ncbi.nlm.nih.gov/pubmed/20674699
29. Blaivas JG, Flisser AJ, Bleustein CB, et al. Periurethral masses: etiology and diagnosis in a large series of women. Obstet Gynecol 2004 May;103(5 Pt 1):842-7. http://www.ncbi.nlm.nih.gov/pubmed/15121554

30. Touijer AK, Dalbagni G. Role of voided urine cytology in diagnosing primary urethral carcinoma. Urology 2004 Jan;63(1):33-5.
http://www.ncbi.nlm.nih.gov/pubmed/14751342
31. Gakis G, Efstathiou JA, Morgan T. et al. Impact of synchronous bladder cancer on recurrence-free survival after surgical treatment for primary urethral cancer: Results of the International Collaboration on Primary Urethral Carcinoma (ICPUC). J Urol 2014;191(4 suppl):176-7.
http://www.jurology.com/article/S0022-5347(14)00930-6/abstract
32. Donat SM, Wei DC, McGuire MS, et al. The efficacy of transurethral biopsy for predicting the long-term clinical impact of prostatic invasive bladder cancer. J Urol 2001 May;165(5):1580-4.
http://www.ncbi.nlm.nih.gov/pubmed/11342921
33. Gourtsoyianni S, Hudolin T, Sala E, et al. MRI at the completion of chemoradiotherapy can accurately evaluate the extent of disease in women with advanced urethral carcinoma undergoing anterior pelvic exenteration. Clin Radiol 2011 Nov;66(11):1072-8.
http://www.ncbi.nlm.nih.gov/pubmed/21839430
34. Kim B, Kawashima A, LeRoy AJ. Imaging of the male urethra. Semin Ultrasound CT MR 2007 Aug;28(4):258-73.
http://www.ncbi.nlm.nih.gov/pubmed/17874650
35. Neitlich JD, Foster HE Jr, Glickman MG, et al. Detection of urethral diverticula in women: comparison of a high resolution fast spin echo technique with double balloon urethrography. J Urol 1998 Feb;159(2):408-10.
http://www.ncbi.nlm.nih.gov/pubmed/9649250
36. Ryu J, Kim B. MR imaging of the male and female urethra. Radiographics 2001 Sep-Oct;21(5): 1169-85.
http://www.ncbi.nlm.nih.gov/pubmed/11553824
37. Stewart SB, Leder RA, Inman BA. Imaging tumors of the penis and urethra. Urol Clin North Am 2010 Aug;37(3):353-67.
http://www.ncbi.nlm.nih.gov/pubmed/20674692
38. Picozzi S, Ricci C, Gaeta M, et al. Upper urinary tract recurrence following radical cystectomy for bladder cancer: a meta-analysis on 13,185 patients. J Urol 2012 Dec;188(6):2046-54.
http://www.ncbi.nlm.nih.gov/pubmed/23083867
39. Dayyani F, Pettaway CA, Kamat AM, et al. Retrospective analysis of survival outcomes and the role of cisplatin-based chemotherapy in patients with urethral carcinomas referred to medical oncologists. Urol Oncol 2013 Oct;31(7):1171-7.
http://www.ncbi.nlm.nih.gov/pubmed/22534087
40. Gakis G, Daneshmand S, Efstathiou JA, et al A. Prognostic factors and outcomes after definitive treatment for primary urethral cancer: Results of the International Collaboration on Primary Urethral Carcinoma. J Urol 2013;189(4 suppl):e388.
http://www.jurology.com/article/S0022-5347(13)00798-2/abstract
41. Campbell SC WP, Surgery of penile and urethral carcinoma, in *Urology*, K.L. Wein AJ, Novick AC, Partin AW, Peters CA, (Eds). 2007, Saunders Elsevier: Philadelphia. p. 993-1022.
42. Carroll PR, Dixon CM. Surgical anatomy of the male and female urethra. Urol Clin North Am 1992 May;19(2):339-46.
http://www.ncbi.nlm.nih.gov/pubmed/1574824
43. Garden AS, Zagars GK, Delclos L. Primary carcinoma of the female urethra. Results of radiation therapy. Cancer 1993 May:71(10):3102-8.
http://www.ncbi.nlm.nih.gov/pubmed/8490839
44. Champ CE, Hegarty SE, Shen X, et al. Prognostic factors and outcomes after definitive treatment of female urethral cancer: a population-based analysis. Urology 2012 Aug;80(2):374-81.
http://www.ncbi.nlm.nih.gov/pubmed/22857759
45. Dalbagni G, Zhang ZF, Lacombe L, et al. Male urethral carcinoma: analysis of treatment outcome. Urology 1999 Jun;53(6):1126-32.
http://www.ncbi.nlm.nih.gov/pubmed/10367840
46. Smith Y, Hadway P, Ahmed S, et al. Penile-preserving surgery for male distal urethral carcinoma. BJU Int 2007 Jul;100(1):82-7.
http://www.ncbi.nlm.nih.gov/pubmed/17488307
47. Pedrosa JA, Amstutz SP, Bihrle R, et al. Distal urethrectomy for localized penile squamous carcinoma in situ extending into the urethra: an updated series. Int Urol Nephrol 2014 Aug;46(8):1551-5.
http://www.ncbi.nlm.nih.gov/pubmed/24633698

48. DiMarco DS, Dimarco CS, Zincke H, et al. Surgical treatment for local control of female urethral carcinoma. Urol Oncol 2004 Sep-Oct;22(5):404-9.
http://www.ncbi.nlm.nih.gov/pubmed/15464921
49. DiMarco DS, DiMarco CS, Zincke H, et al. Outcome of surgical treatment for primary malignant melanoma of the female urethra. J Urol 2004 Feb;171(2 Pt 1):765-7.
http://www.ncbi.nlm.nih.gov/pubmed/14713806
50. Shim JS, Oh MM, Lee JG, et al. Anterior urethrectomy for primary carcinoma of the female urethra mimicking a urethral caruncle. Int Neurourol J 2013 Dec;17(4):197-9.
http://www.ncbi.nlm.nih.gov/pubmed/24466468
51. Milosevic MF, Warde PR, Banerjee D, et al. Urethral carcinoma in women: results of treatment with primary radiotherapy. Radiother Oncol 2000 Jul;56(1):29-35.
http://www.ncbi.nlm.nih.gov/pubmed/10869752
52. Gakis G, Morgan TM, Daneshmand S, et al. Impact of perioperative chemotherapy on survival in patients with advanced primary urethral cancer: Results of the international collaboration on primary urethral carcinoma. J Clin Oncol 2014 (ASCO Meeting Abstracts); 32(15 suppl): 4587.
http://meetinglibrary.asco.org/content/130264-144.
53. Kent M, Zinman L, Girshovich L, et al. Combined chemoradiation as primary treatment for invasive male urethral cancer. Urol. 2014 Aug. pii: S0022-5347(14)04143-3. doi: 10.1016/j.juro.2014.07.105. [Epub ahead of print].
http://www.ncbi.nlm.nih.gov/pubmed/25088950
54. Gakis G. Editorial Comment to Docetaxel, cisplatin and 5-fluorouracil chemotherapy with concurrent radiation for unresectable advanced urethral carcinoma. Int J Urol 2014 Apr;21(4):424-5.
http://www.ncbi.nlm.nih.gov/pubmed/24251884
55. Itoh J, Mitsuzuka K, Kimura S, et al. Docetaxel, cisplatin and 5-fluorouracil chemotherapy with concurrent radiation for unresectable advanced urethral carcinoma. Int J Urol 2014 Apr;21(4):422-4.
http://www.ncbi.nlm.nih.gov/pubmed/24251859
56. Hara I, Hikosaka S, Eto H, et al. Successful treatment for squamous cell carcinoma of the female urethra with combined radio- and chemotherapy. Int J Urol 2004 Aug;11(8):678-82.
http://www.ncbi.nlm.nih.gov/pubmed/15285764
57. Cohen MS, Triaca V, Billmeyer B, et al. Coordinated chemoradiation therapy with genital preservation for the treatment of primary invasive carcinoma of the male urethra. J Urol 2008 Feb;179(2):536-41;discussion 541.
http://www.ncbi.nlm.nih.gov/pubmed/18076921
58. Palou Redorta J, Schatteman P, Huguet Pérez J, et al. Intravesical instillations with bacillus calmette guérin for the treatment of carcinoma in situ involving prostatic ducts. Eur Urol 2006 May;49(5): 834-8;discussion 838.
http://www.ncbi.nlm.nih.gov/pubmed/16426729
59. Taylor JH, Davis J, Schellhammer P. Long-term follow-up of intravesical bacillus Calmette-Guérin treatment for superficial transitional-cell carcinoma of the bladder involving the prostatic urethra. Clin Genitourin Cancer 2007 Sep;5(6):386-9.
http://www.ncbi.nlm.nih.gov/pubmed/17956711
60. Gofrit ON, Pode D, Pizov G, et al. Prostatic urothelial carcinoma: is transurethral prostatectomy necessary before bacillus Calmette-Guérin immunotherapy? BJU Int 2009 Apr;103(7):905-8.
http://www.ncbi.nlm.nih.gov/pubmed/19021623
61. Njinou Ngninkeu B, Lorge F, Moulin P, et al. Transitional cell carcinoma involving the prostate: a clinicopathological retrospective study of 76 cases. J Urol 2003 Jan;169(1):149-52.
http://www.ncbi.nlm.nih.gov/pubmed/12478124
62. Palou J, Baniel J, Klotz L, et al. Urothelial carcinoma of the prostate. Urology 2007 Jan;69(1 Suppl): 50-61.
http://www.ncbi.nlm.nih.gov/pubmed/17280908
63. Hillyard RW Jr, Ladaga L, Schellhammer PF. Superficial transitional cell carcinoma of the bladder associated with mucosal involvement of the prostatic urethra: results of treatment with intravesical bacillus Calmette-Guerin. J Urol 1988 Feb;139(2):290-3.
http://www.ncbi.nlm.nih.gov/pubmed/3339727
64. Solsona E, Iborra I, Ricós JV, et al. The prostate involvement as prognostic factor in patients with superficial bladder tumors. J Urol 1995 Nov;154(5):1710-3.
http://www.ncbi.nlm.nih.gov/pubmed/7563328

65. Vazina A, Dugi D, Shariat SF, et al. Stage specific lymph node metastasis mapping in radical cystectomy specimens. J Urol 2004 May;171(5):1830-4. http://www.ncbi.nlm.nih.gov/pubmed/15076287

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 publically accessible through the European Association of Urology website: http://www.uroweb.org/guidelines/. This guidelines document was developed with the financial support of the European Association of Urology. No external sources of funding and support have been involved. The EAU is a non-profit organisation and funding is limited to administrative assistance and travel and meeting expenses. No honoraria or other reimbursements have been provided.