

EAU Guidelines on Primary Urethral Carcinoma

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1. INTRODUCTION

1.1 Aims and scope

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

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

1.2 Panel composition

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

1.3 Publication history and summary of changes

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

1.3.1 Summary of changes

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

Key changes for the 2015 publication:

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

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

6.2 Predictors of survival in primary urethral carcinoma

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

7.1 Treatment of localised primary urethral carcinoma in males

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

7.2.2 Radiotherapy

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

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

Recommendations	LE	GR
Use cisplatin-based chemotherapeutic regimens with curative intent prior to surgery.	4	C
In locally advanced SCC of the urethra, offer the combination of curative radiotherapy with radiosensitising chemotherapy for genital preservation.	4	C

SCC = squamous cell carcinoma; UC = urethral carcinoma.

2. METHODS

2.1 Data identification

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

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

2.2 Review

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

2.3 Future goals

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

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

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

3. EPIDEMIOLOGY, AETIOLOGY AND PATHOLOGY

3.1 Epidemiology

Primary UC is considered a rare cancer, accounting for < 1% of all malignancies [5] (ICD-O3 topography code: C68.0 [6]).

In early 2008, the prevalence of UC in the 27 EU countries was 4,292 cases with an estimated annual incidence of 655 new cases [7]. The age-standardised ratio was 1.1 per million inhabitants (1.6/million in men and 0.6/million in women; with a male to female ratio of 2.9) [7]. There were differences between European regions; potentially caused by registration or classification [7]. Likewise, in an analysis of the Surveillance, Epidemiology and End Results (SEER) database, the incidence of primary UC peaked in the ≥ 75 years age group (7.6/million). The age-standardised rate was 4.3/million in men and 1.5/million in women, and was almost negligible in those aged < 55 years (0.2/million) [8].

3.2 Aetiology

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

3.3 Histopathology

Both the Surveillance of Rare Cancers in Europe (RARECARE) project and SEER database have reported that urothelial carcinoma of the urethra is the predominant histological type of primary urethral cancer (54-65%), followed by SCC (16-22%) and adenocarcinoma (AC) (10-16%) [7, 8]. A recent SEER analysis of 2,065 men with primary urethral cancer (mean age: 73 years) found that urothelial carcinoma was most common (78%), and SCC (12%) and AC (5%) were significantly less frequent [24]. In women, a recent report of the Dutch National Cancer Registry on primary urethral cancer reported that urothelial carcinoma occurred in 45% of cases, followed by AC in 29%, SCC in 19%, and other histological entities in 6% [25].

4. STAGING AND CLASSIFICATION SYSTEMS

4.1 Tumor, Node, Metastasis (TNM) staging system

In men and women, UC is classified according to the 7th edition of the TNM classification [6] (Table 4.1). It should be noted that there is a separate TNM staging system for prostatic UC [6]. Of note, for cancers occurring in urethral diverticulum, stage T2 is not applicable as urethral diverticula are lacking periurethral muscle [26].

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

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

4.2 Tumour grade

The former World Health Organization (WHO) grading system of 1973 which differentiated urothelial carcinomas into three different grades (G1-G3) has been replaced by the grading system of 2004 that differentiates urothelial UC into papillary urothelial neoplasm of low malignant potential (PUNLMP), low grade and high grade. Non-urothelial UC is graded by a trinomial system that differentiates between well-differentiated (G1), moderately-differentiated (G2), and poorly-differentiated tumours (G3). Table 4.2 lists the different grading systems according to the WHO 1973 and 2004 systems [27].

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

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

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

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

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

5. DIAGNOSTIC EVALUATION AND STAGING

5.1 History

When becoming clinically apparent, most patients (45-57%) with primary UC present with symptoms associated with locally advanced disease (T3/T4) [26-28]. At initial presentation visible haematuria or bloody urethral discharge is reported in up to 62% of the cases. Further symptoms of locally advanced disease include; an extraurethral mass (52%), bladder outlet obstruction (48%), pelvic pain (33%), urethrocutaneous fistula (10%), abscess formation (5%) or dyspareunia [28].

5.2 Clinical examination

In men, physical examination should comprise palpation of the external genitalia for suspicious indurations or masses and digital rectal examination [29]. In women, further pelvic examination with careful inspection and palpation of the urethra should be performed, especially in those with primary onset of irritative or obstructive voiding. In addition, bimanual examination, when necessary under general anaesthesia, should be performed for local clinical staging and to exclude the presence of colorectal or gynaecological malignancies. Bilateral inguinal palpation should be conducted to assess the presence of enlarged lymph nodes, describing location, size and mobility [30].

5.3 Urinary cytology

The role of urinary cytology in primary UC is limited, and its sensitivity ranges between 55% and 59% [31]. Detection rates depend on the underlying histological entity. In male patients, the sensitivity for UC and SCC was reported to be 80% and 50%, respectively, whereas in female patients sensitivity was found to be 77% for SCC and 50% for UC.

5.4 Diagnostic urethroscopy and biopsy

Diagnostic urethroscopy and biopsy enables primary assessment of a urethral tumour in terms of tumour extent, location and underlying histology [29]. To enable accurate pathological assessment of surgical margins, biopsy sites (proximal/distal end) should be marked and sent together with clinical information to the pathologist.

Careful cystoscopic examination is necessary to exclude the presence of concomitant bladder tumours [3, 32]. A cold-cup biopsy enables accurate tissue retrieval for histological analysis and avoids artificial tissue damage. In patients with larger lesions, transurethral resection (optionally in men under penile blood arrest using a tourniquet) can be performed for histological diagnosis. In patients with suspected UC of the prostatic urethra or ducts, resectoscope loop biopsy of the prostatic urethra (at 5 and 7 o'clock positions from the bladder neck and distally around the area of the verumontanum) can contribute to an improved detection rate [33].

5.5 Radiological imaging

Radiological imaging of UC aims to assess local tumour extent and to detect lymphatic and distant metastatic spread. For local staging, there is increasing evidence that magnetic resonance imaging (MRI) is an accurate tool for monitoring tumour response to neoadjuvant chemoradiotherapy and evaluating the extent of local disease prior to exenterative surgery [34]. Imaging for regional lymph node metastases should concentrate on inguinal and pelvic lymph nodes, using either MRI or CT. Distant staging should concentrate on chest and liver, with CT of the thorax and abdomen in all patients with invasive disease (\geq cT1N0M0) [34-38]. If imaging of the remainder of the urothelium is required, then CT should include CT urography with an excretory phase [39].

5.6 Regional lymph nodes

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

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

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

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

CT = computed tomography; MRI = magnetic resonance imaging.

6. PROGNOSIS

6.1 Long-term survival after primary urethral carcinoma

According to the RARECARE project, the mean 1- and 5-year overall survival (OS) in patients with UC in Europe is 71% and 54%, respectively [7]. With longer follow-up, a SEER analysis of 1,615 cases reported median 5- and 10-year OS rates of 46% and 29%, respectively. Cancer-specific survival (CSS) at 5 and 10 years was 68% and 60%, respectively [8].

6.2 Predictors of survival in primary urethral carcinoma

In Europe, mean 5-year OS does not substantially differ between the sexes [7]. Predictors of decreased survival in patients with primary UC are:

- advanced age (\geq 65 years) and black race [7, 45];
- stage, grade, nodal involvement [41] and metastasis [24];
- tumour size and proximal tumour location [24];
- extent of surgical treatment and treatment modality [24, 45];
- underlying histology [7, 25, 45];
- presence of concomitant bladder cancer [32].

Some limitations have to be taken into account in the interpretation of these results. In the Dutch study, the numbers were low ($n = 91$) [26]. In the large SEER database ($n = 2,046$), therapy is not well specified in relation to survival [25]. Finally, in contrast to the RARECARE project [7], the opposite findings were reported in the SEER database in relation to the role of histology on survival in male patients [45].

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

7. DISEASE MANAGEMENT

7.1 Treatment of localised primary urethral carcinoma in males

Previously, treatment of male anterior UC has followed the procedure for penile cancer, with aggressive surgical excision of the primary lesion with a wide safety margin [29]. Distal urethral tumours exhibit significantly improved survival rates compared with proximal tumours [46]. Therefore, optimising treatment of distal UC has become the focus of clinicians to improve functional outcome and quality of life, while preserving oncological safety. A retrospective series found no evidence of local recurrence, even with < 5 mm resection margins (median follow-up: 17-37 months), in men with pT1-3N0-2 anterior UC treated with well-defined penis-preserving surgery and additional iliac/inguinal lymphadenectomy for clinically suspected lymph node disease [47]. This suggests that prognosis is mainly determined by nodal stage. Similar results for the feasibility of penile-preserving surgery have also been reported in a recent series [48].

Summary of evidence	LE
In distal urethral tumours performing a partial urethrectomy with a minimal safety margin does not increase the risk of local recurrence.	3

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

7.2 Treatment of localised urethral carcinoma in females

7.2.1 Urethrectomy and urethra-sparing surgery

In women with localised UC, to provide the highest chance of local cure, primary radical urethrectomy should remove all the periurethral tissue from the bulbocavernosus muscle bilaterally and distally, with a cylinder of all adjacent soft tissue up to the pubic symphysis and bladder neck. Bladder neck closure via an appendicovesicostomy for primary anterior urethral lesions has been shown to provide satisfactory functional results in women [29].

Recent series have reported outcomes in women with mainly anterior UC undergoing primary treatment with urethra-sparing surgery or radiotherapy, compared to primary urethrectomy, with the aim of maintaining integrity and function of the lower urinary tract [49-51]. In long-term series with a median follow-up of 153-175 months, local recurrence rates in women undergoing partial urethrectomy with intraoperative frozen section analysis were 22-60%, and distal sleeve resection of > 2 cm resulted in secondary urinary incontinence in 42% of patients who required additional reconstructive surgery [50].

Ablative surgical techniques, i.e., transurethral resection (TUR) or laser, used for small distal UC, have also resulted in a considerable local failure rate of 16%, with a CSS rate of 50%. This emphasises the critical role of local tumour control in women with distal UC to prevent local and systemic progression [49].

7.2.2 Radiotherapy

In women, radiotherapy was investigated in several older long-term series with a medium follow-up of 91-105 months [44, 47]. With a median cumulative dose of 65 Gy (range: 40-106 Gy), the 5-year local control rate was 64% and 7-year CSS was 49% [44]. Most local failures (95%) occurred within the first two years after primary treatment [47]. The extent of urethral tumour involvement was found to be the only parameter independently associated with local tumour control but the type of radiotherapy (external beam radiotherapy [EBRT] vs. interstitial brachytherapy) was not [44]. In one study, the addition of brachytherapy to EBRT reduced the risk of local recurrence by a factor of 4.2 [52]. Of note, pelvic toxicity in those achieving local control was considerable (49%), including urethral stenosis, fistula, necrosis, and cystitis and/or haemorrhage, with 30% of the reported complications graded as severe [44].

Summary of evidence	LE
In anterior tumours, urethra-sparing surgery and local radiotherapy represent alternatives to primary urethrectomy but are associated with increased risk of tumour recurrence and local toxicity.	3

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

7.3 Multimodal treatment in advanced urethral carcinoma in both genders

7.3.1 Preoperative platinum-based chemotherapy

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

In a series of 39 patients treated with perioperative platinum-based chemotherapy for advanced primary UC, preoperative chemotherapy was found to be associated with improved progression-free and OS compared to surgery followed by adjuvant chemotherapy [53]. Another series reported outcomes in 44 patients with advanced primary UC treated with specific cisplatin-based polychemotherapeutic regimens according to the underlying histology. The overall response rate for the various regimens was 72% and the median OS 32 months. Patients who underwent surgery after chemotherapy had significantly improved OS compared with those who were managed with chemotherapy alone [40].

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

The clinical feasibility of preoperative local radiotherapy with concurrent radiosensitising chemotherapy as an alternative to surgery in locally advanced SCC has been reported in several recent series. This approach offers a potential for genital preservation [53–58]. The largest and recently updated series reported outcomes in 25 patients with primary locally advanced SCC of the urethra treated with two cycles of 5-fluorouracil and mitomycin C with concurrent EBRT. A complete response to primary chemoradiotherapy was observed in ~80%. The 5-year overall- and disease-specific survival was 52% and 68%, respectively. In this updated series, salvage surgery initiated only in non-responders or in case of local failure was not reported to be associated with improved survival [54].

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

Recommendations	LE	GR
Discuss treatment of patients with locally advanced urethral carcinoma within a multidisciplinary team of urologists, radio-oncologists and oncologists.	4	A
Use cisplatin-based chemotherapeutic regimens with curative intent prior to surgery.	4	C
In locally advanced SCC of the urethra, offer the combination of curative radiotherapy with radiosensitising chemotherapy for genital preservation.	4	C

SCC = squamous cell carcinoma

7.4 Treatment of urothelial carcinoma of the prostate

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

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

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

Recommendations	LE	GR
Offer a urethra-sparing approach with TUR and BCG to patients with non-invasive urethral carcinoma or carcinoma <i>in situ</i> of the prostatic urethra and prostatic ducts.	3	C
In patients with non-invasive UC or carcinoma <i>in situ</i> , perform a prior TUR of the prostate to improve response to BCG.	3	C
In patients not responding to BCG, or in patients with extensive ductal or stromal involvement, perform a cystoprostatectomy with extended pelvic lymphadenectomy.	3	C

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

8. FOLLOW-UP

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

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