EAU Guidelines on

Urothelial Carcinoma of the Upper Urinary Tract

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European
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1. INTRODUCTION

1.1 Aim and objectives

The European Association of Urology (EAU) Non-muscle-invasive Bladder Cancer (NMIBC) Guidelines Panel has compiled these clinical guidelines to provide urologists with evidence-based information and recommendations for the management of urothelial carcinoma of the upper urinary tract (UTUC). Separate EAU guidelines documents are available addressing non-muscle-invasive bladder cancer [1], muscle-invasive and metastatic bladder cancer (MIBC) [2], and primary urethral carcinoma [3].

It must be emphasised that clinical guidelines present the best evidence available to the experts but following guideline recommendations will not necessarily result in the best outcome. Guidelines can never replace clinical expertise when making treatment decisions for individual patients, but rather help to focus decisions - also taking personal values and 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 European Association of Urology (EAU) Guidelines Panel on NMIBC consists of an international multidisciplinary group of clinicians, including urologists, uro-oncologists, a radiologist, a pathologist and a statistician. Members of this panel have been selected based on their expertise and to represent the professionals treating patients suspected of harbouring urothelial carcinoma. All experts involved in the production of this document have submitted potential conflict of interest statements, which can be viewed on the EAU website Uroweb: http://uroweb.org/guideline/upper-urinary-tracturothelial-cell-carcinoma/.

1.3 Available publications

A quick reference document (Pocket guidelines) is available in print and in a number of versions for mobile devices, presenting the main findings of the UTUC Guidelines. These are abridged versions which may require consultation together with the full text version. Several scientific publications are available as are a number of translations of all versions of the EAU UTUC Guidelines. All documents are accessible through the EAU website Uroweb: http://uroweb.org/guideline/upper-urinary-tract-urothelial-cell-carcinoma/.

1.4 Publication history & summary of changes

The first EAU guidelines on UTUC were published in 2011. The 2017 EAU guidelines on UTUC present a limited update of the 2016 version.

1.4.1 Summary of changes

The literature for the complete document has been assessed and updated, whenever relevant.
Conclusions and recommendations have been rephrased and added to throughout the current document.

Key changes for the 2017 print:

New section 3.3.1.1 - Summary of evidence for Chapter 3 (Epidemiology, aetiology and pathology) has been added.

3.3.1.1 Summary of evidence for histology and classification

Summary of evidence	LE
A small proportion of upper tract urothelial carcinoma belong to the tumour spectrum of the hereditary non-polyposis colorectal cancer.	3

New section 5.3 - Summary of evidence section has been added to the Guidelines for the diagnosis of upper tract urothelial carcinoma.

5.3 Summary of evidence and guidelines for the diagnosis of upper tract urothelial carcinoma

Summary of evidence	LE
The diagnosis of urothelial carcinoma of the upper urinary depends on computed tomography urography.	2
Selective urinary cytology has high sensitivity in high-grade tumours including carcinoma *in situ*.	3

New section 7.1.2.4 – Summary of evidence section has been added to the Guidelines for radical nephroureterectomy.

7.1.2.4 Summary of evidence and guidelines for radical nephroureterectomy

Summary of evidence	LE
Radical nephroureterectomy is the standard in high-risk upper tract urothelial carcinoma, regardless of tumour location.	2
Open and laparoscopic approaches have equivalent efficacy and safety in T1–2/N0 upper tract urothelial carcinoma.	2

2. METHODS

2.1 Data identification

Standard procedure for EAU Guidelines includes an annual assessment of newly published literature in the field to guide future updates. For the 2017 UTUC Guidelines, new and relevant evidence has been identified, collated and appraised through a structured assessment of the literature. A broad and comprehensive scoping exercise covering all areas of the entire guideline was performed. Excluded from the search were basic research studies, case series, reports and editorial comments. Only articles published in the English language, addressing adults were included. The search was restricted to articles published between June 1st 2015 and April 22nd 2016. Databases searched included Pubmed, Ovid, EMBASE and both the Cochrane Central Register of Controlled Trials and the Cochrane Database of Systematic Reviews. After deduplication, a total of 973 unique records were identified, retrieved and screened for relevance. A detailed search strategy is available online: http://uroweb.org/guideline/upper-urinary-tract-urothelial-cell-carcinoma/?type=appendicespublications.

References used in this text are assessed according to their level of evidence (LE) and Guidelines are given a grade of recommendation (GR), according to a classification system modified from the Oxford Centre for Evidence-Based Medicine Levels of Evidence [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 online at the above address.

2.2 Review

This document was peer-reviewed prior to publication in 2016.

2.3 Future goals

The results on ongoing and new systematic reviews will be included in the 2018 update of the UTUC Guidelines. These reviews are performed using standard Cochrane systematic review methodology: http://www.cochranelibrary.com/about/about-cochrane-systematic-reviews.html.

Ongoing systematic reviews:

- Oncological outcomes of laparoscopic/robotic radical nephroureterectomy versus open radical nephroureterectomy for upper tract urothelial carcinoma: an EAU Guidelines systematic review [5].
- What are the benefits and harms of lymph node dissection (LND) during radical nephroureterectomy for upper tract urothelial carcinoma (UTUC)? [6].

3. EPIDEMIOLOGY, AETIOLOGY AND PATHOLOGY

3.1 Epidemiology

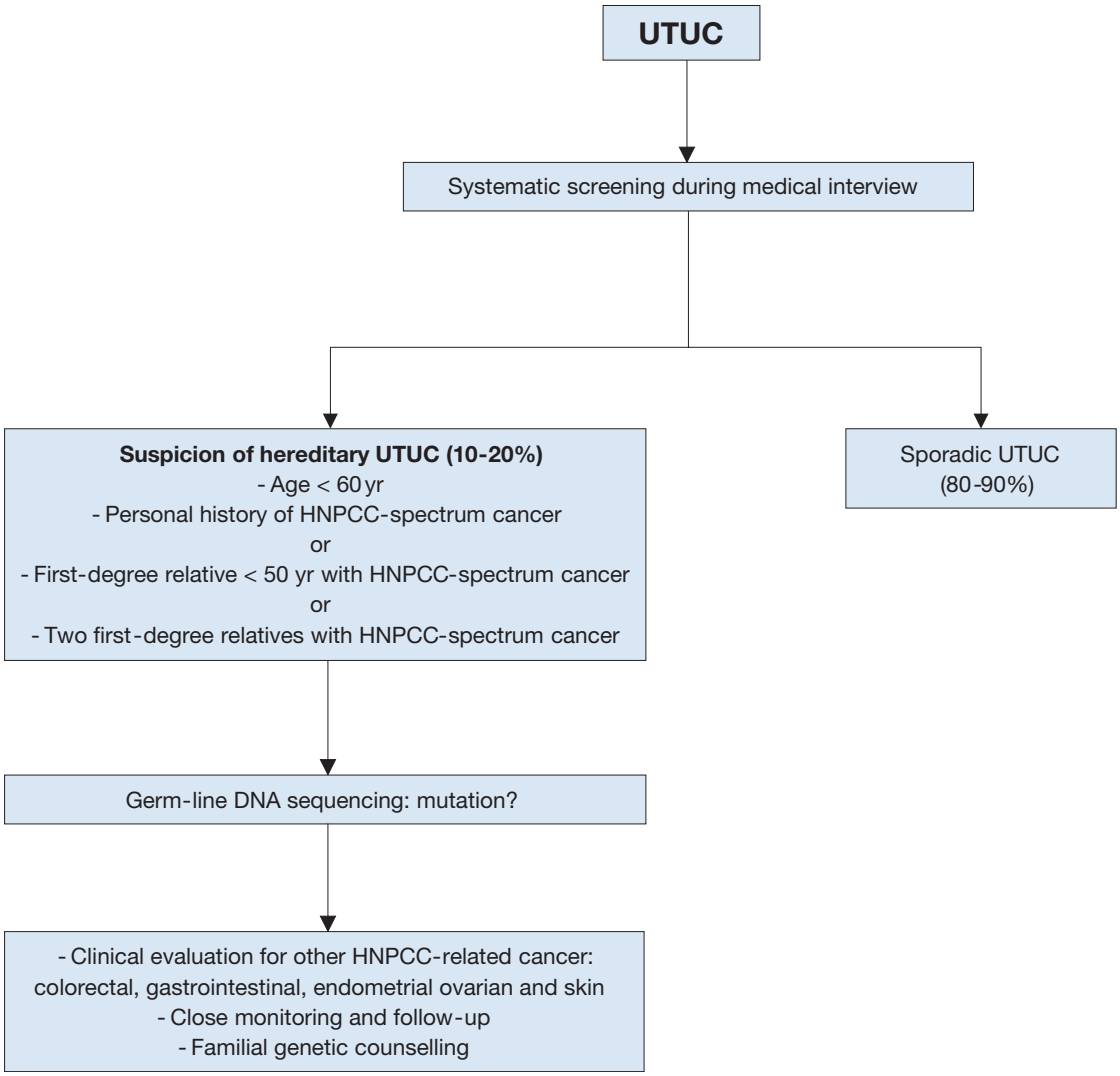
Urothelial carcinomas (UCs) are the fifth most common tumours [7]. They can be located in the lower (bladder and urethra) or upper (pyelocaliceal cavities and ureter) urinary tract. Bladder tumours account for 90-95% of UCs and are the most common malignancy of the urinary tract [8]. In contrast, UTUC are uncommon and account for only 5-10% of UCs [9, 10]. Pyelocaliceal tumours are about twice as common as ureteral tumours.

In 17% of cases, concurrent bladder cancer is present [11]. Recurrence in the bladder occurs in 22-47% of UTUC patients [12], compared with 2-6% in the contralateral upper tract [13, 14].

Approximately 60% of UTUC are invasive at diagnosis compared with 15-25% of bladder tumours [8, 15]. Upper tract urothelial carcinomas have a peak incidence in people aged 70 to 90 years and are three times more common in men [16, 17].

Familial/hereditary UTUC are linked to hereditary non-polyposis colorectal carcinoma (HNPCC) [18], which can be screened for during an interview (Figure 3.1) [19]. Patients should undergo DNA sequencing to identify hereditary cancers misclassified as sporadic if they fulfil the criteria for HNPCC [18, 20].

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



HNPCC = hereditary non-polyposis colorectal carcinoma.

3.2 Risk factors

Various environmental risk factors contribute to UTUC development [21, 22]. Tobacco exposure increases the relative risk from 2.5 to 7 [21, 23]. Historically, UTUC 'amino tumours' were related to occupational exposure to carcinogenic aromatic amines. The odds ratio of developing UC after exposure to aromatic amines is 8.3 [21, 22]. Upper tract urothelial carcinoma caused by phenacetin consumption almost disappeared after the product was banned in the 1970s [22].

Upper tract urothelial carcinoma often present after a bladder cancer. The average duration of exposure needed to develop UTUC is ~7 years, with a latency of ~20 years following termination of exposure.

Several studies have revealed the carcinogenic potential of aristolochic acid contained in *Aristolochia fangchi* and *Aristolochia clematis*. The aristolochic acid derivative dA-aristolactam causes a specific mutation in the p53 gene at codon 139, which occurs mainly in patients with nephropathy due to Chinese herbs or Balkan endemic nephropathy [22, 24, 25].

There is a high incidence of UTUC in Taiwan, especially on the South-west coast which represents 20-25% of UCs in the region [22, 25]. There is a possible association of UTUC with blackfoot disease and arsenic exposure in drinking water in this population [22, 25, 26].

Differences in the ability to counteract carcinogens may contribute to host susceptibility to UTUC. Some genetic polymorphisms are associated with an increased risk of cancer or faster disease progression, which introduces variability in the inter-individual susceptibility to the risk factors previously mentioned. Upper tract urothelial carcinoma may share some risk factors or molecular disruption pathways with bladder UC. Two UTUC-specific polymorphisms have been reported [27, 28].

3.3 Histology and classification

*3.3.1 **Histological types***

Upper tract urothelial carcinoma with pure non-urothelial histology is an exception [29, 30] but variants are present in ~25% of cases [31, 32]. These variants always correspond to high-grade tumours with worse prognosis compared to pure UC. Squamous cell carcinoma of the upper urinary tract represents < 10% of pyelocaliceal tumours and is even rarer within the ureter. Squamous cell carcinoma of the urinary tract can be associated with chronic inflammatory and infectious diseases arising from urolithiasis [33, 34]. Other variants are: micropapillary, sarcomatoid carcinomas and lymphoepithelioma [33, 34].

3.3.1.1 Summary of evidence for histology and classification

Summary of evidence	LE
A small proportion of upper tract urothelial carcinoma belong to the tumour spectrum of the hereditary non-polyposis colorectal cancer.	3

4. STAGING AND CLASSIFICATION SYSTEMS

4.1 Classification

The classification and morphology of UTUC and bladder carcinoma are similar [8]. It is possible to distinguish between non-invasive papillary tumours (papillary urothelial tumours of low malignant potential, and low-grade and high-grade papillary UC), flat lesions (carcinoma *in situ* [CIS]), and invasive carcinoma. As in bladder tumours, non-urothelial differentiation has been identified as an adverse risk factor [35].

4.2 Tumour Node Metastasis staging

The Tumour Node Metastasis (TNM) classification is shown in Table 4.1 [36]. The regional lymph nodes that should be considered are the hilar, abdominal para-aortic, and paracaval nodes, and, for the ureter, the intrapelvic nodes. Laterality does not affect N classification.

A subclassification with pT3a and pT3b has been suggested, but is not in the officially accepted pTNM staging system [31, 37, 38]. Renal pelvic pT3 subclassification may discriminate between microscopic infiltration of the renal parenchyma (pT3a) and macroscopic infiltration or invasion of peripelvic adipose tissue. pT3b UTUC is more likely to be associated with aggressive pathologic features and disease recurrence [31, 37].

Table 4.1: TNM classification 2017 for upper tract urothelial carcinoma [36]

T - Primary tumour	
TX	Primary tumour cannot be assessed
T0	No evidence of primary tumour
Ta	Non-invasive papillary carcinoma
Tis	Carcinoma *in situ*
T1	Tumour invades subepithelial connective tissue
T2	Tumour invades muscularis
T3	(Renal pelvis) Tumour invades beyond muscularis into peripelvic fat or renal parenchyma (Ureter) Tumour invades beyond muscularis into periureteric fat
T4	Tumour invades adjacent organs or through the kidney into perinephric fat
N - Regional lymph nodes	
NX	Regional lymph nodes cannot be assessed
N0	No regional lymph node metastasis
N1	Metastasis in a single lymph node 2 cm or less in the greatest dimension
N2	Metastasis in a single lymph node more than 2 cm, or multiple lymph nodes
M - Distant metastasis	
M0	No distant metastasis
M1	Distant metastasis

4.3 Histological grading

In 2004, the WHO and the International Society of Urological Pathology published a new histological classification of urothelial carcinomas which provides a different patient stratification between individual categories compared to the older 1973 WHO classification [39, 40]. Recently an update of the 2004 WHO grading classification was published [41], but the following guidelines are still based on the 1973 and 2004 WHO classifications [39, 40].

Only few tumours of low malignant potential are found in the upper urinary tract, [33, 34]. pT2 tumours should be treated as high-grade disease.

4.4 Guidelines for staging and classification systems

Recommendations	LE	GR
Classify the depths of invasion (staging) according to Tumour Node Metastasis classification, 8th edition.	3	A
Classify flat, high-grade tumours, confined to the mucosa, as carcinoma *in situ* (Tis).	3	A
Use the World Health Organization 1973 and 2004 grading systems for the histological classification of upper tract urothelial carcinoma.	3	A

5. DIAGNOSIS

5.1 Symptoms

The most common symptom is visible- or non-visible haematuria (70-80%) [42, 43]. Flank pain occurs in 20-40% of cases, and a lumbar mass in 10-20% [44, 45]. Systemic symptoms (including anorexia, weight loss, malaise, fatigue, fever, night sweats, or cough) are associated with UTUC and should prompt more rigorous evaluation for metastatic disease [44, 45].

5.2 Diagnosis

*5.2.1 **Imaging***

5.2.1.1 Computed tomography urography

Computed tomography (CT) urography has the highest diagnostic accuracy for UTUC of all the clinically available imaging techniques [45]. The sensitivity of CT urography for UTUC is 0.67-1.0 and the specificity is 0.93-0.99 according to the technique used [21, 46-51]. Epithelial 'flat lesions' without mass effect or urothelial thickening are not visible with CT [52].

Computed tomography urography is defined as CT examination of the kidneys, ureters and bladder following the administration of intravenous contrast material [21, 53]. Rapid acquisition of thin sections provides high-resolution isotropic images that can be viewed in multiple planes to assist with diagnosis without loss of resolution. Computed-tomography urography usually includes several phases of acquisition following administration of intravenous contrast media [21, 54].

The secondary sign of hydronephrosis is associated with advanced disease and poor oncological outcome [21, 53, 55, 56]. The presence of enlarged lymph nodes is highly predictive of metastasis in UTUC [21].

5.2.1.2 Magnetic resonance imaging

Magnetic resonance urography (MRU) is indicated in patients who cannot undergo CT urography, usually when radiation or iodinated contrast media are contraindicated [57]. The sensitivity of MRU is 0.75 after contrast injection for tumours < 2 cm [57]. The use of MRU with gadolinium-based contrast media should be limited in patients with severe renal impairment (< 30 mL/min creatinine clearance), due to the risk of nephrogenic systemic fibrosis. Computed tomography urography is generally preferred over MRU for diagnosing UTUC.

*5.2.2 **Cystoscopy and urinary cytology***

Positive urine cytology is suggestive of UTUC when bladder cystoscopy is normal, provided that no CIS is detected in the bladder or prostatic urethra [8, 58]. Cytology is less sensitive for UTUC than for bladder tumours. It should be performed in the upper tract (*in situ* cytology) [59].

Retrograde ureteropyelography is an option to evaluate UTUC [21, 49, 60, 61] but is now mostly used in conjunction with ureteroscopy and not as a stand-alone diagnostic technique due to similar diagnostic accuracy when compared with CT urography for UTUC [49]. Urinary cytology of the renal cavities and ureteral lumina is preferable before application of contrast agent for retrograde ureteropyelography, because the latter may cause deterioration of cytological specimens [59, 60].

The sensitivity of fluorescence *in situ* hybridisation (FISH) for molecular abnormalities characteristic of UTUC parallels its performance in bladder cancer [62]. However, its use may be limited by the preponderance of low-grade recurrent disease in the population undergoing surveillance and kidney-sparing therapy for UTUC [63, 64]. FISH currently has limited value for the surveillance of UTUC [63, 64].

*5.2.3 **Diagnostic ureteroscopy***

Flexible ureteroscopy is used to visualise the ureter, renal pelvis and collecting system and biopsy suspicious lesions. Ureteroscopic biopsies can determine tumour grade in 90% of cases with a low false-negative rate, regardless of sample size [65]. Under-grading may occur from diagnostic biopsy, making intensive follow-up necessary if a kidney-sparing treatment is chosen [66]. Ureteroscopy also facilitates selective ureteral sampling for cytology to detect carcinoma *in situ* [60, 67, 68].

Flexible ureteroscopy is especially useful for diagnostic uncertainty, if kidney-sparing treatment is considered, or in patients with a solitary kidney. Additional information can be provided by ureteroscopy with- or without biopsy. Combining ureteroscopic biopsy grade, imaging findings such as hydronephrosis, and urinary cytology, may help in the decision-making process between radical nephroureterectomy (RNU) and endoscopic treatment [67, 69].

Technical developments in flexible ureteroscopes and the use of novel imaging techniques improve visualisation and the diagnosis of flat lesions [70]. Narrow-band imaging is the most promising technique to date but the results are preliminary [69, 71]. Table 5.3 lists the recommendations for diagnosis.

5.3 Summary of evidence and guidelines for the diagnosis of upper tract urothelial carcinoma

Summary of evidence	LE
The diagnosis of upper tract urothelial carcinoma depends on computed tomography urography.	2
Selective urinary cytology has high sensitivity in high-grade tumours including carcinoma *in situ*.	3

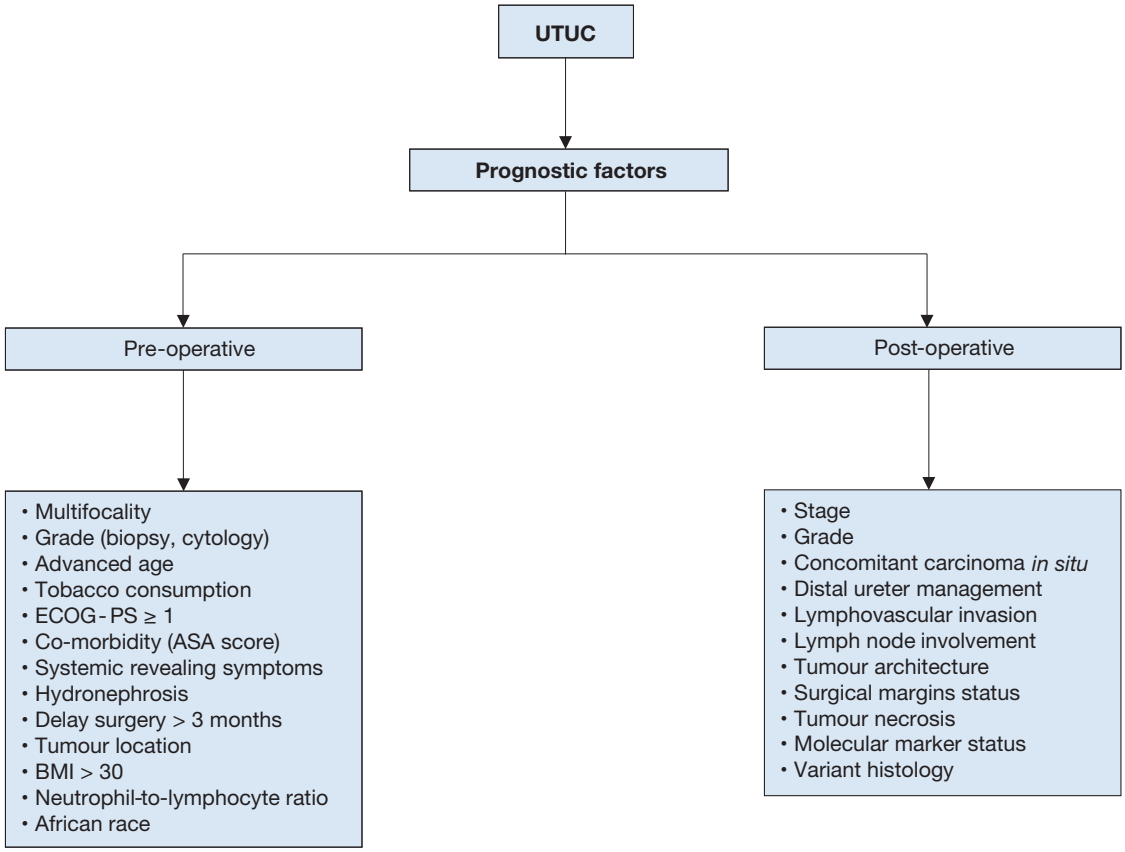
Recommendations	GR
Perform urinary cytology as part of a standard diagnostic work-up.	A
Perform a cystoscopy to rule out concomitant bladder tumour.	A
Perform a computed tomography urography for the diagnostic work-up.	A
Use diagnostic ureteroscopy and biopsy in cases where additional information will impact treatment decisions.	C

6. PROGNOSIS

6.1 Prognostic factors

Upper tract urothelial carcinomas that invade the muscle wall usually have a poor prognosis. The five-year specific survival is < 50% for patients with pT2/pT3 tumours and < 10% for those with pT4 [71-73]. The main prognostic factors are briefly listed below; Figure 6.1 presents a more exhaustive list.

Figure 6.1: Upper tract urothelial carcinoma - Prognostic factors



ASA = American Society of Anesthesiologists; BMI = body mass index;

ECOG = Eastern Cooperative Oncology Group; PS = performance score.

*6.1.1 **Pre-operative factors***

6.1.1.1 Age and sex

Gender is no longer considered an independent prognostic factor influencing UTUC mortality [16, 73, 74]. Older age at the time of RNU is independently associated with decreased cancer-specific survival [73, 75] (LE: 3). Many elderly patients can be cured with RNU [76], suggesting that age alone is an inadequate indicator of outcome [75, 76]. Despite its association with survival, age alone should not prevent a potentially curable approach.

6.1.1.2 Ethnicity

One multicentre study did not show any difference between races [77] but population-based studies have indicated that African-American patients have worse outcomes compared to other ethnicities [76, 78] (LE: 3).

6.1.1.3 Tobacco consumption

Being a smoker at diagnosis increases the risk for disease recurrence and mortality after RNU [79, 80] as well as recurrence within the bladder [81] (LE: 3).

6.1.1.4 Tumour location

Initial location of the UTUC is a prognostic factor in some studies [82-84] (LE: 3). After adjustment for the effect of tumour stage, patients with ureteral and/or multifocal tumours seem to have a worse prognosis than those with renal pelvic tumours [73, 83-86].

6.1.1.5 Surgical delay

A delay between diagnosis of an invasive tumour and its removal may increase the risk of disease progression. Once a decision regarding RNU has been made the procedure should be carried-out within twelve weeks [87-90] (LE: 3).

6.1.1.6 Other

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

*6.1.2 **Post-operative factors***

6.1.2.1 Tumour stage and grade

The primary recognised prognostic factors are tumour stage and grade [21, 67, 73, 97].

6.1.2.2 Lymph node involvement

Lymph node metastases and extranodal extension are powerful predictor of survival outcomes in UTUC [98]. Lymph node dissection (LND) performed at the time of RNU allows for optimal tumour staging [99, 100] (LE: 3). Its curative role remains debated.

6.1.2.3 Lymphovascular invasion

Lymphovascular invasion is present in ~20% of UTUC and is an independent predictor of survival [101, 102]. Lymphovascular invasion status should be specifically reported in the pathological reports of all UTUC specimens [101, 103] (LE: 3).

6.1.2.4 Surgical margins

Positive soft tissue surgical margin after RNU is a significant factor for developing UTUC recurrence. Pathologists should look for, and report, positive margins at the level of ureteral transection, bladder cuff, and around the tumour soft tissue margin [104] (LE: 3).

6.1.2.5 Pathological factors

Extensive tumour necrosis (> 10% of the tumour area) is an independent prognostic predictor in patients who undergo RNU [105, 106] (LE: 3). The architecture of UTUC is also a strong prognosticator with sessile growth pattern being associated with worse outcome [107, 108] (LE: 3). Concomitant CIS in organ-confined UTUC, and a history of bladder CIS are associated with a higher risk of disease recurrence and cancer-specific mortality [109-111] (LE: 3). Similar to lower tract UC, concomitant CIS is an independent predictor of worse outcomes in organ-confined disease [112].

6.2 Molecular markers

Several studies have investigated the prognostic impact of markers related to cell adhesion (E-cadherin and CD24), cell differentiation (Snail and epidermal growth factor receptor), angiogenesis (hypoxia-inducible factor-1α and metalloproteinases), cell proliferation (Ki67), epithelial-mesenchymal transition (Snail), mitosis (Aurora-A), apoptosis (Bcl-2 and survivin), vascular invasion (RON), c-met protein (MET) and mTOR pathway [21, 73, 113-117]. Microsatellite instability (MSI) is an independent molecular prognostic marker [118] and can help detect germline mutations and hereditary cancers [18].

The rarity of UTUC means that the main limitations of the above studies were their retrospective nature and small sample size. None of the markers have fulfilled the criteria necessary to support their introduction in daily clinical decision-making.

6.3 Predictive tools

Accurate predictive tools are rare for UTUC. There are two models in a pre-operative setting: one in locally advanced cancer that can guide the extent of LND at the time of RNU [119]; and one for selection of non-organ-confined UTUC likely to benefit from RNU [120]. Four nomograms are available predicting survival rates post-operatively, based on standard pathological features [121-125].

6.4 Bladder recurrence

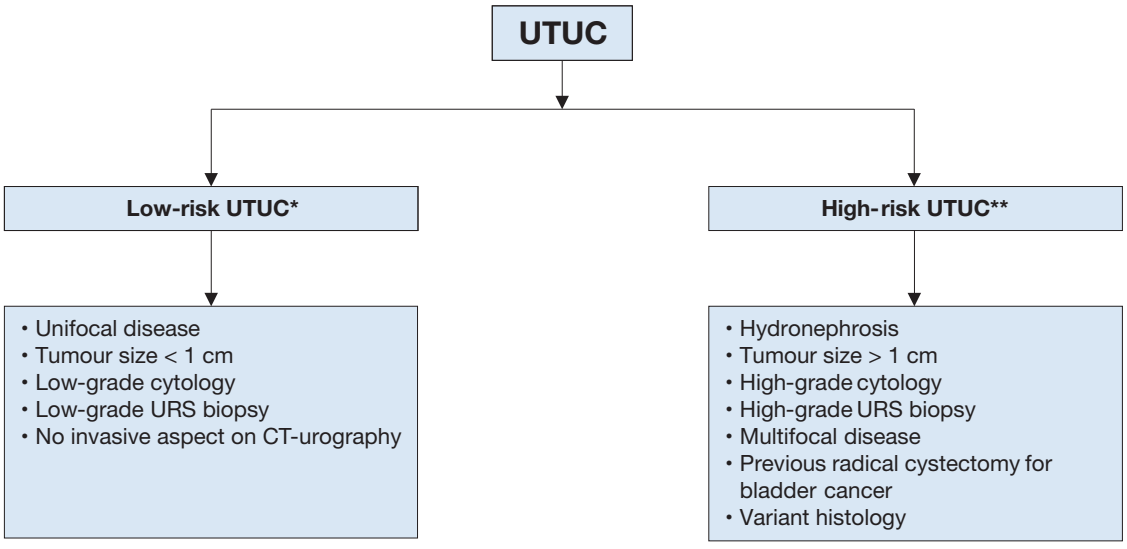
A recent meta-analysis of available data has identified significant predictors of bladder recurrence after RNU [12] (LE: 3). Three categories of predictors of increased risk for bladder recurrence were identified:

- patient-specific factors such as (male gender, previous bladder cancer, pre-operative chronic kidney disease);
- tumour-specific factors such as (positive pre-operative urinary cytology, ureteral location, multifocality, invasive pT stage, necrosis);
- treatment-specific factors such as (laparoscopic approach, extravesical bladder cuff removal, positive surgical margins) [12].

6.5 Risk stratification

As tumour stage is difficult to assert clinically in UTUC, It is useful to 'risk stratify' UTUC between low- and high-risk tumours to identify those that are more suitable for kidney-sparing treatment rather than radical extirpative surgery [126, 127] (Figure 6.2).

Figure 6.2: Pre-intervention risk stratification of upper tract urothelial carcinoma



*All of these factors need to be present

** *Any of these factors need to be present*

CTU = computed tomography urography; URS = ureterorenoscopy.

6.6 Summary of evidence and guidelines for prognosis

Summary of evidence	LE
Age, sex and ethnicity are no longer considered as independent prognostic factors.	3
The primary recognised post-operative prognostic factors are tumour stage and grade, extranodal extension and lymphovascular invasion.	3

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

7. DISEASE MANAGEMENT

7.1 Localised disease

*7.1.1 **Kidney-sparing surgery***

Kidney-sparing surgery (KSS) for low-risk UTUC (Section 7.1.1.4) allows sparing the morbidity associated with radical surgery, without compromising oncological outcomes and kidney function [128]. In low-risk cancers it is the primary approach and survival is similar after KSS versus RNU [129]. This option should therefore be discussed in all low-risk cases, irrespective of the status of the contralateral kidney [21, 130, 131]. In high-risk tumours it can be considered in imperative cases (i.e. renal insufficiency or solitary functional kidney).

7.1.1.1 Ureteroscopy

Endoscopic ablation can be considered in patients with clinically low-risk cancer in the following situations [132, 133]:

- laser generator [134] and pliers are available for biopsies [133, 135] (LE: 3);
- in case a flexible ureteroscope is available (rather than a rigid ureteroscope);
- the patient is informed of the need for closer, more stringent, surveillance;
- complete tumour resection can be achieved.

Nevertheless, a risk of under-staging and under-grading remains with endoscopic management.

7.1.1.2 Percutaneous access

Percutaneous management can be considered for low-risk UTUC in the renal cavities [21, 133, 136] (LE: 3). This may be offered for low-risk tumours in the lower caliceal system that are inaccessible or difficult to manage by flexible ureteroscopy. However, this approach is being used less due to the availability of improved materials and advances in distal-tip deflection of recent ureteroscopes [21, 133, 136].

7.1.1.3 Surgical open approach

Segmental ureteral resection with wide margins provides adequate pathological specimens for staging and grading, while preserving the ipsilateral kidney. A lymphadenectomy can also be achieved during segmental ureteral resection.

Complete distal ureterectomy with neocystostomy are indicated for low-risk tumours in the distal ureter that cannot be removed completely endoscopically, and for high-risk tumours when kidney-sparing surgery for renal function preservation is necessary [21, 137, 138] (LE: 3).

Segmental resection of the iliac and lumbar ureter is associated with higher failure rates than for the distal pelvic ureter [21, 137, 138] (LE: 3).

Partial pyelectomy or partial nephrectomy is almost never indicated. Open resection of tumours of the renal pelvis or calices has almost disappeared.

7.1.1.4 *Guidelines for kidney-sparing management of upper tract urothelial carcinoma*

Recommendations	GR
Offer kidney-sparing management as primary treatment option to patients with low-risk tumour and two functional kidneys.	C
Offer kidney-sparing management in patients with solitary kidney and/or impaired renal function, providing it will not compromise the oncological outcome. This decision will have to be made on a case-by-case basis, engaging the patient in a shared decision-making process.	C
Offer a kidney-sparing approach in high-risk cancers for distal ureteral tumours and in imperative cases (solitary kidney and/or impaired renal function).	C
Use a laser for endoscopic treatment of upper tract urothelial carcinoma.	C

7.1.1.5 *Adjuvant topical agents*

The antegrade instillation of bacillus Calmette-Guérin (BCG) vaccine or mitomycin C in the upper urinary tract by percutaneous nephrostomy via a three-valve system open at 20 cm (after complete tumour eradication) is feasible after kidney-sparing management or for treatment of CIS [139] (LE: 3). Retrograde instillation through a ureteric catheter is also used. The reflux obtained from a double-J stent has been used, but is not advisable since it often does not reach the renal pelvis [140].

7.1.2 ***Radical nephroureterectomy***

Open RNU with bladder cuff excision is the standard treatment for high-risk UTUC, regardless of tumour location [15] (LE: 3). Radical nephroureterectomy must comply with oncological principles, that is preventing tumour seeding by avoidance of entry into the urinary tract during resection [15].

Resection of the distal ureter and its orifice is performed because there is a considerable risk of tumour recurrence in this area. After removal of the proximal ureter, it is difficult to image or approach it by endoscopy [21, 137, 141].

Several techniques have been considered to simplify distal ureter resection, including pluck technique, stripping, transurethral resection of the intramural ureter, and intussusception [13, 21, 141]. Except for ureteral stripping, none of these techniques is inferior to bladder cuff excision [75-77, 83] (LE: 3).

7.1.2.1 *Laparoscopic radical nephroureterectomy*

Retroperitoneal metastatic dissemination and metastasis along the trocar pathway following manipulation of large tumours in a pneumoperitoneal environment have been reported in few cases [142, 143].
Several precautions may lower the risk of tumour spillage:

- avoid entering the urinary tract;
- avoid direct contact between instruments and the tumour;
- laparoscopic RNU must take place in a closed system. Avoid morcellation of the tumour and use an endobag for tumour extraction;
- the kidney and ureter must be removed *en-bloc* with the bladder cuff;
- invasive or large (T3/T4 and/or N+/M+) tumours are contraindications for laparoscopic RNU until proven otherwise.

Laparoscopic RNU is safe in experienced hands when adhering to strict oncologic principles. There is a tendency towards equivalent oncological outcomes after laparoscopic or open RNU [21, 143-147] (LE: 3).

Only one prospective randomised study has shown that laparoscopic RNU is not inferior to open RNU for non-invasive UTUC. In contrast, oncological outcomes were in favour of the open approach in pT3 and/or high-grade tumours [148] (LE: 2). Oncological outcomes after RNU have not changed significantly over the past three decades despite staging and refinements in staging and surgical technique [149] (LE: 3). A robot-assisted laparoscopic approach can be considered, but solid data are still lacking [150].

7.1.2.2 *Lymph node dissection*

The anatomic sites of lymph node drainage have not been clearly defined yet. The use of a LND template is likely to have a greater impact on patient survival than the number of removed lymph nodes [134].

Lymph node dissection appears to be unnecessary in cases of TaT1 UTUC because lymph node retrieval is reported in only 2.2% of T1 versus 16% of pT2-4 tumours [98]. An increase in the probability of lymph-node-positive disease is related to pT classification [100]. However, it is likely that the true rate of node-positive disease has been under-reported because these data are retrospective.

Despite available studies evaluating templates to date, it is not possible to standardise indication

or extent of LND [151, 152]. Lymph node dissection can be achieved following lymphatic drainage as follows: LND on the side of the affected ureter, retroperitoneal LND for higher ureteral tumour and/or tumour of the renal pelvis (i.e. right side: border vena cava or right side of the aorta; and left side: border aorta) [21, 98].

7.1.2.3 Adjuvant bladder instillation

The rate of bladder recurrence after RNU for UTUC is 22-47% [12, 153]. Two prospective randomised trials have demonstrated that a single post-operative dose of intravesical chemotherapy (mitomycin C, pirarubicin) immediately after surgery reduces the risk of bladder tumour recurrence within the first year post-RNU [154-156] (LE: 1b).

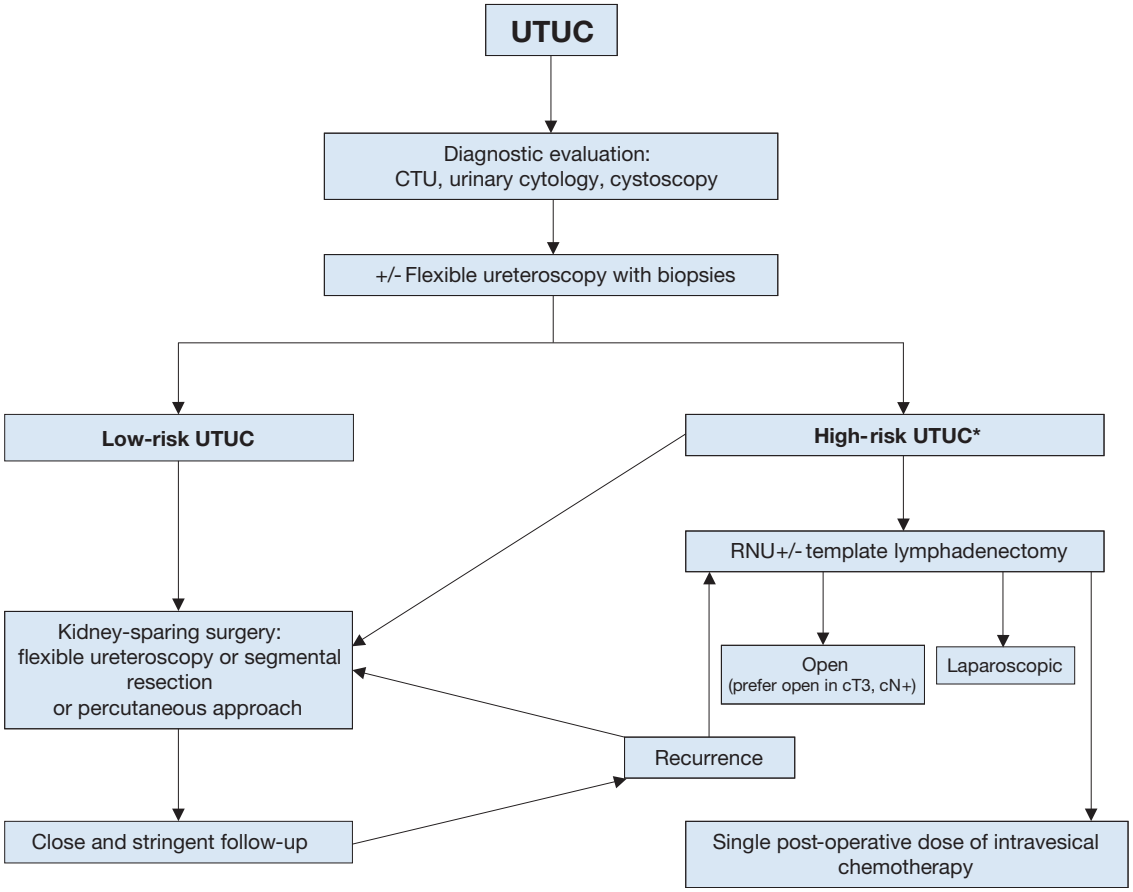
7.1.2.4 Summary of evidence and guidelines for radical nephroureterectomy

Summary of evidence	**LE**
Radical nephroureterectomy is the standard in high-risk upper tract urothelial carcinoma, regardless of tumour location.	2
Open and laparoscopic approaches have equivalent efficacy and safety in T1–2/N0 upper tract urothelial carcinoma.	2

Recommendations	**GR**
Perform radical nephroureterectomy in the following situations: • suspicion of infiltrating upper tract urothelial carcinoma on imaging; • high-grade tumour (urinary cytology); • multifocality (with two functional kidneys); • non-invasive but large (> 1 cm) upper tract urothelial carcinoma.	B
Technical steps of radical nephroureterectomy:	
Remove the bladder cuff.	A
Perform a lymphadenectomy in invasive upper tract urothelial carcinoma.	C
Offer a post-operative bladder instillation to lower the bladder recurrence rate.	B

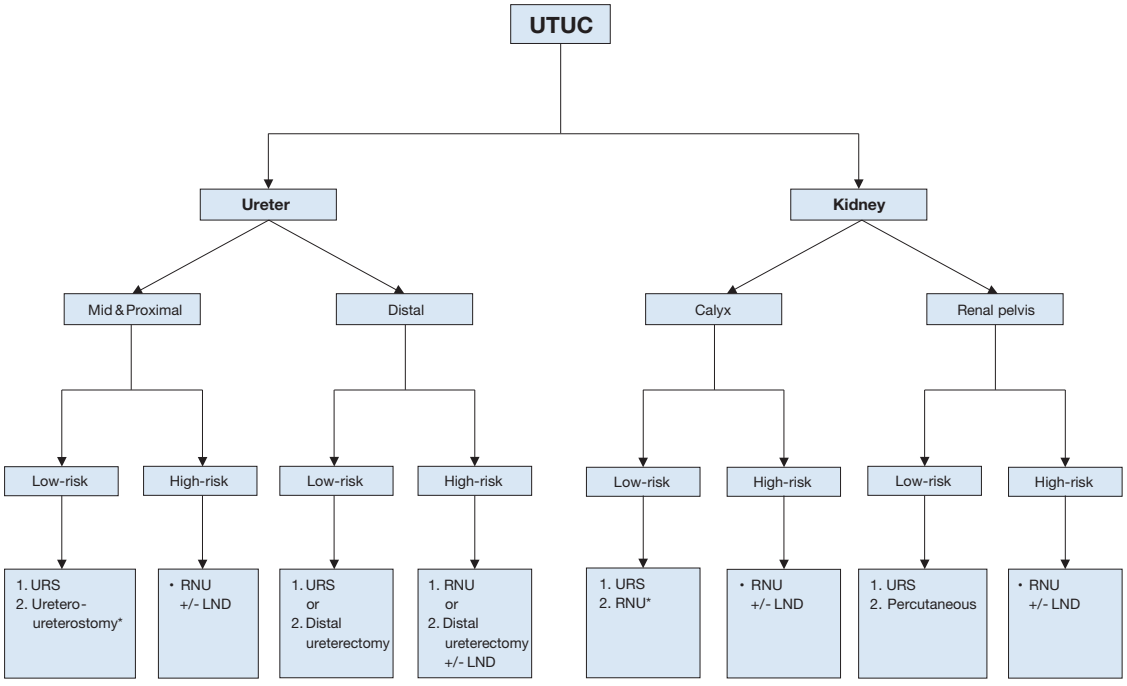
Management is outlined in Figures 7.1 and Figure 7.2.

Figure 7.1: Proposed flowchart for the management of localised upper tract urothelial carcinoma



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

Figure 7.2: Surgical treatment according to location and risk status



1. First treatment option
2. Secondary treatment option

**In case not amendable to endoscopic management.*

7.2 Advanced disease

7.2.1 Radical nephroureterectomy

There is no oncologic benefit for RNU in patients with metastatic UTUC except for palliative considerations [15, 100] (LE: 3).

7.2.2 Systemic chemotherapy

Extrapolating from the bladder cancer literature and small, single centre UTUC studies, platinum-based combination chemotherapy is expected to be efficacious in UTUC. However, there are currently insufficient data upon which to base recommendations.

There are several platinum-based regimens [157], but not all patients can receive adjuvant chemotherapy because of comorbidities and impaired renal function after radical surgery. Chemotherapy-related toxicity, particularly nephrotoxicity from platinum derivatives, may significantly affect survival in patients with post-operative renal dysfunction [158, 159].

There were no adverse effects of neoadjuvant chemotherapy for UTUC in the only study published to date [160], although survival data need to mature and longer follow-up is awaited. Adjuvant chemotherapy can achieve a recurrence-free rate of < 50% [161, 162].

After a recent comprehensive search of studies examining the role of peri-operative chemotherapy for UTUC, there appears to be an overall survival and disease-free survival benefit for cisplatin-based adjuvant chemotherapy [163] (LE: 3). However, there are currently insufficient data to base recommendations on until further evidence from an ongoing prospective trial is available [164].

7.2.3 Radiotherapy

The role of adjuvant radiotherapy is not well defined, neither alone, nor in combination with chemotherapy [21, 165] (LE: 3). It may be of benefit in terms of loco-regional and bladder control in selected patients but data are too scarce to give recommendations.

7.2.4 Summary of evidence and guideline for advanced disease

Summary of evidence	LE
Peri-operative systemic cisplatin-based chemotherapy may provide a survival benefit.	3

Recommendation	LE	GR
In case chemotherapy is offered, a neoadjuvant approach is recommended, as the renal function will decrease after radical nephroureterectomy.	3	C

8. FOLLOW-UP

The risk of disease recurrence and death evolves in the follow-up period after surgery and is less likely with time [166, 167]. Stringent follow-up (Section 8.1) is mandatory to detect metachronous bladder tumours [13], local recurrence, and distant metastases. When RNU is performed, local recurrence is rare and the risk of distant metastases is directly related to the risk factors listed previously.

Surveillance regimens are based on cystoscopy and urinary cytology for > 5 years [11-13]. Bladder recurrence is not a distant recurrence [12]. When kidney-sparing surgery is performed, the ipsilateral UUT requires careful follow-up due to the high risk of disease recurrence [130, 135, 168]. Despite endourological improvements, follow-up after kidney-sparing surgery is difficult; frequent and repeated endoscopic procedures are mandatory. As done in bladder cancer, a second look has been proposed after KSS but is not yet routine practice [169].

8.1 Summary of evidence and guidelines for follow-up of upper tract urothelial carcinoma patients after initial treatment

Summary of evidence	LE
Follow-up is more frequent and more strict in patients who have undergone kidney-sparing treatment compared to radical nephroureterectomy.	3

Recommendations	GR
After radical nephroureterectomy, > five years	
Non-invasive tumour	
Perform cystoscopy/urinary cytology at three months, and then annually.	C
Perform computed tomography urography every year.	C
Invasive tumour	
Perform cystoscopy/urinary cytology at three months, and then annually.	C
Perform computed tomography urography every six months for two years, and then annually.	C
After kidney-sparing management, > five years	
Perform urinary cytology and computed tomography urography at three and six months, and then annually.	C
Perform cystoscopy, ureteroscopy and cytology *in situ* at three and six months, and then every six months for two years, and then annually.	C

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10. CONFLICT OF INTEREST

All members of the Non-Muscle-Invasive Bladder Cancer Guidelines working panel have provided disclosure statements on all relationships that they have that might be perceived to be a potential source of a conflict of interest. This information is publically accessible through the European Association of Urology website: http://uroweb.org/guideline/upper-urinary-tract-urothelial-cell-carcinoma/. This guidelines document was developed with the financial support of the European Association of Urology. No external sources of funding and support have been involved. The EAU is a non-profit organisation, and funding is limited to administrative assistance and travel and meeting expenses. No honoraria or other reimbursements have been provided.