EAU Guidelines on

Urothelial Carcinomas of the Upper Urinary Tract

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European Association of Urology

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1. INTRODUCTION

1.1 Aims and objective

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).

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 European Association of Urology (EAU) Guidelines Panel on NMIBC consists of an international multidisciplinary group of clinicians, including 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-tract-urothelial-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 can be viewed on the EAU website: 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 2016 EAU guidelines on UTUC presents an update of the 2015 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 2016 print:
Changed or new conclusions and recommendations can be found in sections:

- Section 6.2 Molecular markers has been added as a new topic.
- Section 6.4 Bladder recurrence has been added as a new topic.

New recommendations have been included in Chapter 6 - Prognosis

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 lymphocascular invasion.	3

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

MSI = Microsatellite instability.

- In section 7.1.2.1 Laparoscopic radical nephrectomy, the findings of the Systematic review have been included (see below).
- Section 7.2.2 Systemic chemotherapy has been expanded.
- A new algorithm - Figure 7.2 Surgical treatment according to location and risk status - has been included.

2. METHODS

2.1 Data identification

For the 2016 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. The search was limited to studies representing high levels of evidence only (i.e. systematic reviews with meta-analysis, randomised controlled trials, and prospective non-randomised comparative studies only) published in the English language. The search was restricted to articles published during the period from 1st April 2014 to 31st May 2015. Databases covered by the search included Medline, EMBASE and the Cochrane Libraries. A total of 1,040 unique records were identified, retrieved and screened for relevance. The search strategy is published online: http://uroweb.org/guideline/upper-urinary-tract-urothelial-cell-carcinoma/?type=appendices-publications.

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 [1]. 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 as the above address.

2.2 Review

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

2.3 Future goals

The results on ongoing and new systematic reviews will be included in the 2017 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 UTUC.
- What are the oncological outcomes of kidney-sparing surgery versus radical nephroureterectomy for the treatment of upper tract urothelial carcinoma? [2].
- What are the benefits and harms of lymph node dissection (LND) during radical nephroureterectomy for upper tract urothelial carcinoma (UTUC)? [3].

3. EPIDEMIOLOGY, AETIOLOGY AND PATHOLOGY

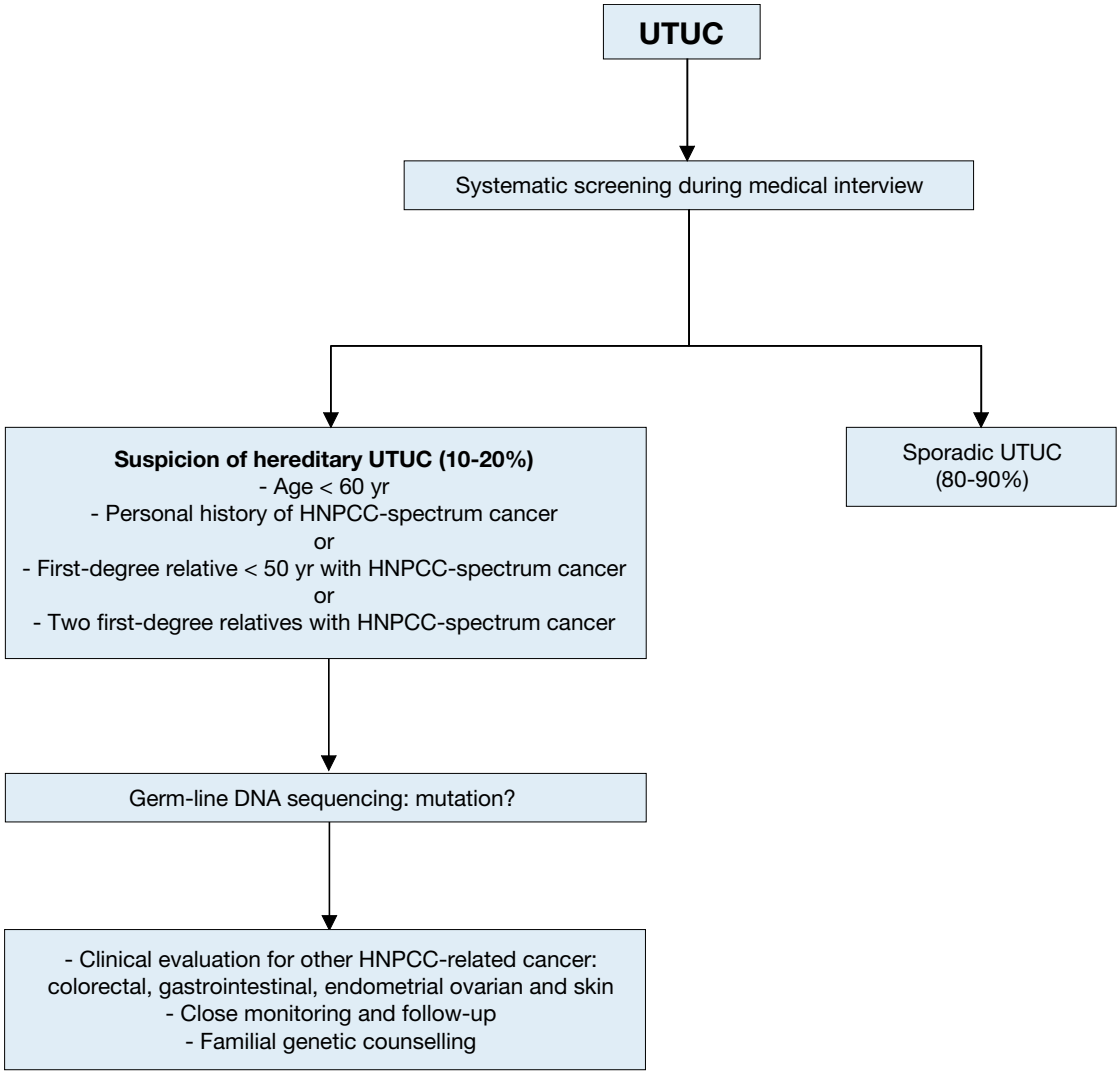
3.1 Epidemiology

Urothelial carcinomas (UCs) are the fifth most common tumours [4]. 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 [5]. In contrast, UTUCs are uncommon and account for only 5-10% of UCs [4, 6]. Pyelocaliceal tumours are about twice as common as ureteral tumours. In 17% of cases, concurrent bladder cancer is present [7]. Recurrence in the bladder occurs in 22-47% of UTUC patients [8], compared with 2-6% in the contralateral upper tract [9, 10].

Approximately 60% of UTUCs are invasive at diagnosis compared with 15-25% of bladder tumours [11, 12]. UTUCs have a peak incidence in people aged 70-90 years and are three times more common in men [13, 14].

Familial/hereditary UTUCs are linked to hereditary non-polyposis colorectal carcinoma (HNPCC) [15], which can be screened for during interview (Figure 3.1) [16]. Patients should undergo DNA sequencing to identify hereditary cancers misclassified as sporadic if they fulfil the criteria for HNPCC [15, 17].

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 [18, 19]. Tobacco exposure increases the relative risk from 2.5 to 7 [20, 21]. Historically, UTUC 'amino tumours' were related to occupational exposure to carcinogenic aromatic amines. However no specific risk factors for UTUC have been suggested compared to bladder cancer.

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. The odds ratio of developing UC after exposure to aromatic amines is 8.3 [19, 21]. Upper tract urothelial tumours caused by phenacetin consumption almost disappeared after the product was banned in the 1970s [19].

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 [19, 22, 23].

There is a high incidence of UTUC in Taiwan, especially on the South-west coast which represents 20-25% of UCs in the region [19, 23]. There is a possible association of UTUC with blackfoot disease and arsenic exposure in drinking water in this population [19, 23, 24].

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. Only two UTUC-specific polymorphisms have been reported [25, 26].

3.3 Histology and classification

3.3.1 ***Histological types***

There are morphological variants of UTUC. These variants always correspond to high-grade tumours with worse prognosis compared to pure UC. Those variants are: micropapillary, plasmacytoid, small cell carcinoma (neuroendocrine) or lymphoepithelial variants [27, 28].

Upper tract urothelial carcinoma with pure non-urothelial histology is an exception [29, 30] but variants are present in ~25% of cases [31] [31, 32]. 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 [27, 28].

4. STAGING AND CLASSIFICATION SYSTEMS

4.1 Classification

The classification and morphology of UTUC and bladder carcinoma are similar [11]. 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.

4.2 Tumour Node Metastasis staging

The Tumour Node Metastasis (TNM) classification is shown in Table 4.1 [33]. 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 in the pTNM staging system [31, 34, 35]. 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 have aggressive pathology and higher risk of disease recurrence [31, 34].

Table 4.1: TNM classification 2009 for upper tract urothelial carcinoma [33]

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 muscle
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 but not more than 5 cm in the greatest dimension or multiple lymph nodes, none more than 5 cm in greatest dimension
N3	Metastasis in a lymph node more than 5 cm in greatest dimension
M - Distant metastasis	
M0	No distant metastasis
M1	Distant metastasis

4.3 Tumour grade

Until 2004, the World Health Organization (WHO) classification of 1973 was used most often, which distinguished only three grades (G1-G3) [36, 37]. The 2004 WHO classification considers histological data to distinguish non-invasive tumours: papillary urothelial neoplasia of low malignant potential, and low-grade and high-grade carcinomas (low grade vs. high grade). Only few tumours of low malignant potential are found in the upper urinary tract [27, 28].

4.4 Guidelines for staging and classification systems

Recommendation	LE	GR
Classify the depths of invasion (staging) according to TNM classification.	3	A
Classify flat, high-grade tumours, confined to the mucosa, as CIS (Tis).	3	A
Use the WHO 1973 and 2004 grading systems for the histological classification of UTUC.	3	A

CIS (Tis) = carcinoma in situ; TNM = Tumour, Node, Metastasis (classification); WHO = World Health Organization.

5. DIAGNOSIS

5.1 Symptoms

The most common symptom is visible- or non-visible haematuria (70-80%) [38, 39]. Flank pain occurs in 20-40% of cases, and a lumbar mass in 10-20% [40, 41]. 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 [40, 41].

5.2 Diagnosis

*5.2.1 **Imaging***

5.2.1.1 Computed tomography urography

Computed tomography urography (CTU) has the highest diagnostic accuracy for the diagnosis of UTUC [41]. The sensitivity of CTU for UTUC is 0.67-1.0 and the specificity is 0.93-0.99 [42-49].

Computed tomography urography is defined as CT examination of the kidneys, ureters and bladder following the administration of intravenous contrast material and includes several phases of image acquisition. [50]. 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 [51, 52].

Flat lesions are not detectable unless they exert a mass effect or cause urothelial thickening [53].

The secondary sign of hydronephrosis is associated with advanced disease and poor oncological outcome [50, 54, 55]. The presence of enlarged lymph nodes is highly predictive of metastasis in UTUC [56].

5.2.1.2 Magnetic resonance imaging

Magnetic resonance urography (MRU) is indicated in patients who cannot undergo CTU, 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 in the bladder or prostatic urethra CIS has been detected [11, 58]. Cytology is less sensitive for UTUC than bladder tumours and it should be performed *in situ* in the renal cavities [59].

Retrograde ureteropyelography remains an option to evaluate UTUCs [43, 60]. 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 UTUCs parallels its performance in bladder cancer [61]. However, its use may be limited by the preponderance of low-

grade recurrent disease in the population undergoing surveillance and minimally invasive therapy for UTUCs [62, 63]. FISH appears to have a limited value for surveillance of UTUCs [62, 63].

*5.2.3 **Diagnostic ureteroscopy***

Flexible ureteroscopy is used to visualise and biopsy the ureter, renal pelvis and collecting system. Such ureteroscopic biopsies can determine tumour grade in 90% of cases with a low false-negative rate, regardless of sample size [64]. Undergrading may occur from diagnostic biopsy, making intensive follow-up necessary if a kidney-sparing treatment is chosen [65]. Ureteroscopy also facilitates selective ureteral sampling for cytology to detect carcinoma *in situ* [60, 66, 67].

Flexible ureteroscopy is especially useful for diagnostic uncertainty, when 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 [66, 68].

Technical developments in flexible ureteroscopes and the use of novel imaging techniques improve visualisation and the diagnosis of flat lesions. Narrow-band imaging is the most promising technique to date but the results are too preliminary [68, 69]. Table 5.1 lists the recommendations for diagnosis.

5.3 Guidelines for the diagnosis of upper tract urothelial carcinomas

Recommendation	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 CT-urography for the diagnostic work-up.	A
Use diagnostic ureteroscopy and biopsy in cases where additional information will impact treatment decisions.	C
Perform retrograde ureteropyelography in case CT-urography or ureteroscopy do no reliably reveal the presence or extent of the tumour.	C

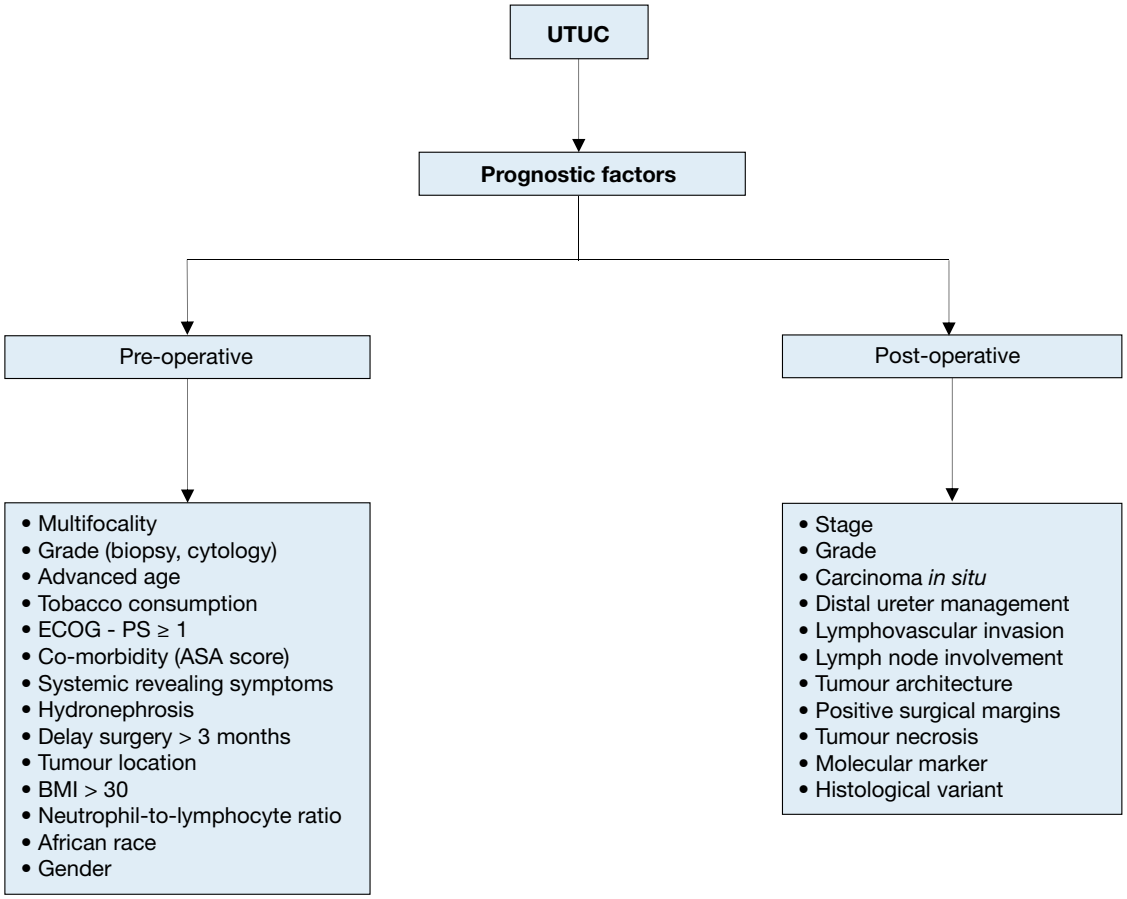
CT-urography = computed tomography urography.

6. PROGNOSIS

6.1 Prognostic factors

Upper tract urothelial carcinomas that invade the muscle wall usually have a poor prognosis. The 5-year specific survival is < 50% for patients with pT2/pT3 tumours and < 10% for those with pT4 [69-71]. The main prognostic factors are briefly listed below; Figure 6.1 presents an 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 **Preoperative factors***

6.1.1.1 Age and sex

Sex is no longer considered an independent prognostic factor influencing UTUC mortality [13, 71, 72]. Older age at the time of RNU is independently associated with decreased cancer-specific survival [71, 73] (LE: 3). Many elderly patients can be cured with RNU [74], suggesting that age alone is an inadequate indicator of outcome [73, 74]. 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 [75] but population-based studies have indicated that African-American patients have worse outcomes compared to other ethnicities [74, 76] (LE: 3).

6.1.1.3 Tobacco consumption

Being a smoker at diagnosis increases the risk for disease recurrence and mortality after RNU [77, 78] as well as increases recurrence within the bladder [79] (LE: 3).

6.1.1.4 Tumour location

Initial location of the UTUC is a prognostic factor [80-82] (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 [71, 81-84].

6.1.1.5 Surgical delay

A delay between diagnosis of an invasive tumour and its removal may increase the risk of disease progression. The time limit from decision for RNU to its performance ranges from 30 days and 3 months [85-88] (LE: 3).

6.1.1.6 Other

The American Society of Anesthesiologists (ASA) score significantly correlates with cancer-specific survival after RNU [89] (LE: 3). The Eastern Cooperative Oncology Group (ECOG) performance status correlates only with overall survival [90]. Obesity and higher body mass index adversely affect cancer-specific outcomes in UTUCs [91, 92] (LE: 3). The pretreatment derived neutrophil-lymphocyte ratio correlates also with higher cancer-specific mortality [93, 94] (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 [66, 71, 95, 96].

6.1.2.2 Lymph node involvement

Extranodal extension is a powerful predictor of clinical outcomes in UTUCs and positive lymph node metastases [97]. Lymph node dissection (LND) performed at the time of RNU allows for optimal tumour staging [98, 99] (LE: 3). Lymph node invasion is an important prognostic factor, indicating metastatic spread to the lymph nodes.

6.1.2.3 Lymphovascular invasion

Lymphovascular invasion is present in ~20% of UTUCs and is an independent predictor of survival [100, 101]. Lymphovascular invasion status should be specifically reported in the pathological reports of all RNU specimens [100, 102] (LE: 3).

6.1.2.4 Surgical margins

Positive soft tissue surgical margin after RNU is a significant factor for developing UTUC metastases. Pathologists should look for, and report, positive margins at the level of ureteral transection, bladder cuff, and around the tumour soft tissue margin [103] (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 [104, 105] (LE: 3). The tissue architecture of UTUC is also a strong prognosticator with sessile growth pattern being associated with worse outcome [106, 107] (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 [108-110] (LE: 3). Similar to lower tract UC, concomitant CIS is an independent predictor of worse outcomes in organ-confined disease [111].

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 [71, 112-117]. Microsatellite instability (MSI) is an independent molecular prognostic marker [118] and can help detect germline mutations and hereditary cancers [15].

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 preoperative 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

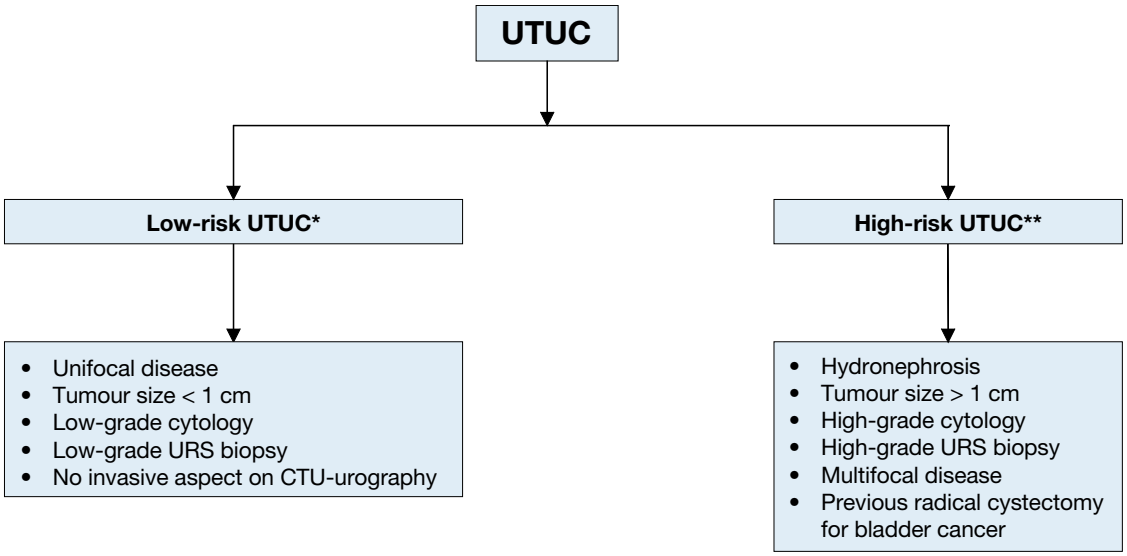
A recent meta-analysis of available data has identified significant predictors of bladder recurrence after RNU [8] (LE: 3). Three categories of predictors of increased risk for bladder recurrence were identified:

- patient-specific factors such as (male gender, previous bladder cancer, preoperative chronic kidney disease);
- tumour-specific factors such as (positive preoperative urinary cytology, ureteral location, multifocality, invasive pT stage, necrosis);
- treatment-specific factors such as (laparoscopic approach, extravesical bladder cuff removal, positive surgical margins) [8].

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 carcinomas



*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 lymphocascular invasion.	3

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

MSI = Microsatellite instability.

7. DISEASE MANAGEMENT

7.1 Localised disease

7.1.1 Kidney-sparing surgery

Kidney-sparing surgery 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. This option should therefore be discussed in all low-risk cases, irrespective of the status of the contralateral kidney [129-131].

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 patient 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 understaging and undergrading remains with endoscopic management.

7.1.1.2 Percutaneous access

Percutaneous management can be considered for low-risk UTUCs in the renal cavities [133, 136, 137] (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. This approach is being used less due to the availability of improved materials and advances in distal-tip deflection of recent ureteroscopes [133, 136, 137].

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 [138-140] (LE: 3).
- Segmental resection of the iliac and lumbar ureter is associated with higher failure rates than for the distal pelvic ureter [138-140] (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
In patients with solitary kidney and/or impaired renal function, offer kidney-sparing management, 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
In high-risk cancers, offer a kidney-sparing approach for distal ureteral tumours and in imperative cases (solitary kidney and/or impaired renal function).	C
Offer kidney-sparing management in case of:	
• Unifocal tumour; • Tumour < 1 cm; • Low-grade tumour; • No evidence of infiltrative lesion on CTU; • Understanding of close follow-up.	B
If treatment is done endoscopically, use a laser.	C

CTU = computed tomography urography.

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 [141] (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 [142].

*7.1.2 **Radical nephroureterectomy***

Open RNU with bladder cuff excision is the standard treatment for high-risk UTUC, regardless of tumour location [12] (LE: 3). Radical nephroureterectomy must comply with oncological principles, that is preventing tumour seeding by avoidance of entry into the urinary tract during resection [12].

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 [129, 138, 143].

Several techniques have been considered to simplify distal ureter resection, including pluck technique, stripping, transurethral resection of the intramural ureter, and intussusception [9, 143, 144]. Except for ureteral stripping, none of these techniques is inferior to bladder cuff excision [73-75, 81] (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 [145, 146].

Several precautions may lower the risk of tumour spillage:

- Avoidance to enter the urinary tract;
- Avoidance of direct contact between instruments and the tumour;
- Laparoscopic RNU must take place in a closed system. Avoidance of morcellation of the tumour and an endobag for tumour extraction should be used;
- 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 [146-152] (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 [153] (LE: 2). Oncological outcomes after RNU have not changed significantly over the past three decades despite staging and refinements in staging and surgical technique [154] (LE: 3). A robot-assisted laparoscopic approach can be can be considered, but solid data are still lacking [155].

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 [97]. An increase in the probability of lymph-node-positive disease is related to pT classification [99]. 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 [156, 157]. LND can be achieved following lymphatic drainage as follows: LND medial to the ureter in ureteropelvic tumour, 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) [96, 97, 129].

7.1.2.3 Adjuvant bladder instillation

The rate of bladder recurrence after RNU for UTUC is 22-47% [8, 158]. 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 [159-161] (LE: 1b).

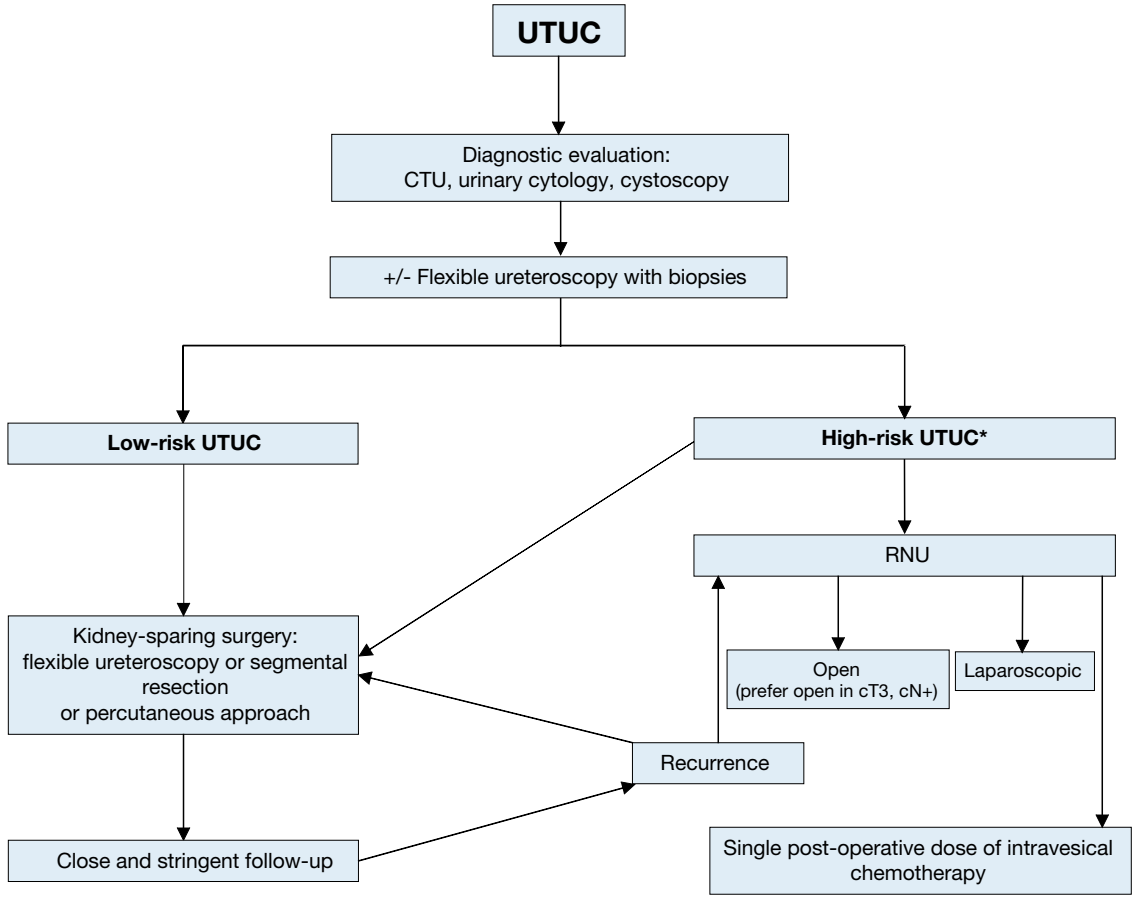
7.1.2.4 Guidelines for radical nephroureterectomy

Recommendations	GR
RNU is the standard in high-risk UTUC, regardless of tumour location.	B
Use RNU in the following situations:	
• Suspicion of infiltrating UTUC on imaging;	B
• High-grade tumour (urinary cytology);	B
• Multifocality (with two functional kidneys);	B
• Non-invasive but large (> 1 cm) UTUC.	B
RNU techniques:	
• Remove the bladder cuff;	A
• Perform a lymphadenectomy in invasive UTUC;	C
• Offer a post-operative bladder instillation to lower the bladder recurrence rate.	B
Open and laparoscopic approaches have equivalent efficacy and safety in T1–T2/N0 UTUCs.	B

RNU = radical nephroureterectomy.

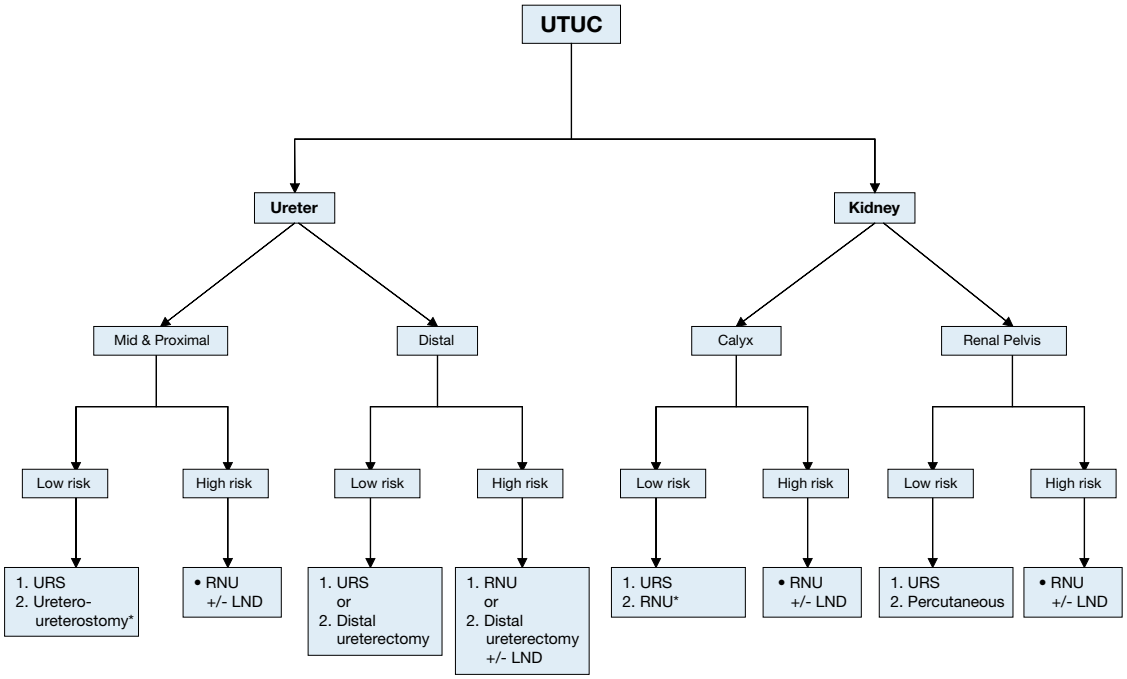
Management is outlined in Figures 7.1 and Figure 7.2.

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 [12, 99] (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 to base recommendations on.

There are several platinum-based regimens [162], 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 [163, 164].

There were no adverse effects of neoadjuvant chemotherapy for UTUCs in the only study published to date [165], although survival data need to mature and longer follow-up is awaited. Adjuvant chemotherapy can achieve a recurrence-free rate of ≤ 50% [166, 167].

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 [168] (LE: 3). However, there are currently insufficient data to base recommendations on until further evidence from an ongoing prospective trial is available [169].

*7.2.3 **Radiotherapy***

The role of adjuvant radiotherapy is not well defined, neither alone, nor in combination with chemotherapy [170, 171] (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 RNU.	3	C

8. FOLLOW-UP

The risk of disease recurrence and death evolves over the follow-up after surgery and is less likely with time [172, 173]. Stringent follow-up (Section 8.1) is mandatory to detect metachronous bladder tumours [9], 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 [7-9]. Bladder recurrence is not a distant recurrence [8]. When kidney-sparing surgery is performed, the ipsilateral UUT requires careful follow-up due to the high risk of disease recurrence [130, 135, 174]. Despite endourological improvements, follow-up after kidney-sparing surgery is difficult; frequent and repeated endoscopic procedures are mandatory.

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 RNU.	3

Recommendations	GR
After RNU, ≥ five years	
Non-invasive tumour	
• Perform cystoscopy/urinary cytology at three months, and then annually.	C
• Perform CT-urography every year.	C
Invasive tumour	
• Perform cystoscopy/urinary cytology at three months, and then annually.	C
• Perform CT-urography every six months for two years, and then annually.	C
After kidney-sparing management, ≥ five years	
• Perform urinary cytology and CTU 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

CT-urography = computed tomography urography; RNU = radical nephroureterectomy.

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10. CONFLICT OF INTEREST

All members of the Upper Urinary Tract Urothelial Carcinomas 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 organization, and funding is limited to administrative assistance and travel and meeting expenses. No honoraria or other reimbursements have been provided.