Guidelines on Urothelial Carcinomas of the Upper Urinary Tract

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European Association of Urology

TABLE OF CONTENTS PAGE

1. INTRODUCTION

Upper tract urothelial carcinoma (UTUC) are relatively uncommon compared to bladder cancer, but 60% of UTUCs are invasive at diagnosis.

1.1 Panel composition

The European Association of Urology (EAU) Guidelines Panel on UTUC 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.

1.2 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 versions. 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://www.uroweb.org/guidelines/online-guidelines/.

1.3 Publication history & summary of changes

The first EAU guidelines on UTUC were published in 2011. The current 2015 EAU guidelines on UTUC present an update of the 2014 version, and provide evidence-based information for clinical management of UTUC.

*1.3.1 **Summary of changes***

A detailed overview of changes for this 2015 print version is posted online.
The literature for the complete document has been assessed and updated, whenever relevant;
Key changes for this 2015 print:

- New algorithms have been included:
  Fig. 3.1: Selection of patients with UTUC for hereditary screening from first medical interview.
  Fig. 6.1: UTUC prognostic factors;
  Fig. 6.2: Risk stratification of UTUC (table presentation in the 2014 print version);
  Fig. 7.1: Proposed flowchart for the management of UTUC was amended.

Recommendations have been rephrased and added to throughout the current document.
In Table 7.1. Guidelines for kidney sparing management of low-risk UTUC, the open surgical approach options have been expanded, not resulting in a change in the grade of recommendation (GR).

Surgical open approach	
Renal pelvis or calyces: Partial pyelectomy or partial nephrectomy is seldom indicated.	C
Ureter - Mid & proximal: Ureteroureterostomy is indicated for tumours that cannot be removed completely endoscopically.	C
Ureter - Distal: Complete distal ureterectomy and neocystostomy are indicated for tumours in the distal ureter that cannot be removed completely endoscopically.	C

2. METHODS

2.1 Data identification

Medline was searched for urothelial malignancies and UTUC management using combinations of the following: *urinary tract cancer, urothelial carcinoma, upper urinary tract, renal pelvis, ureter, chemotherapy, nephroureterectomy, adjuvant treatment, neoadjuvant treatment, recurrence, risk factors, nomogram*, and *survival*, with a November 2013 cut-off. Articles were selected using the following criteria: evolution of concepts, intermediate- and long-term clinical outcomes, study quality, and relevance. To facilitate evaluation of information quality, level of evidence (LE) and grade of recommendation (GR) were inserted according to evidence-based medicine (EBM) [1].

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

2.2 Review

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

3. EPIDEMIOLOGY, AETIOLOGY AND PATHOLOGY

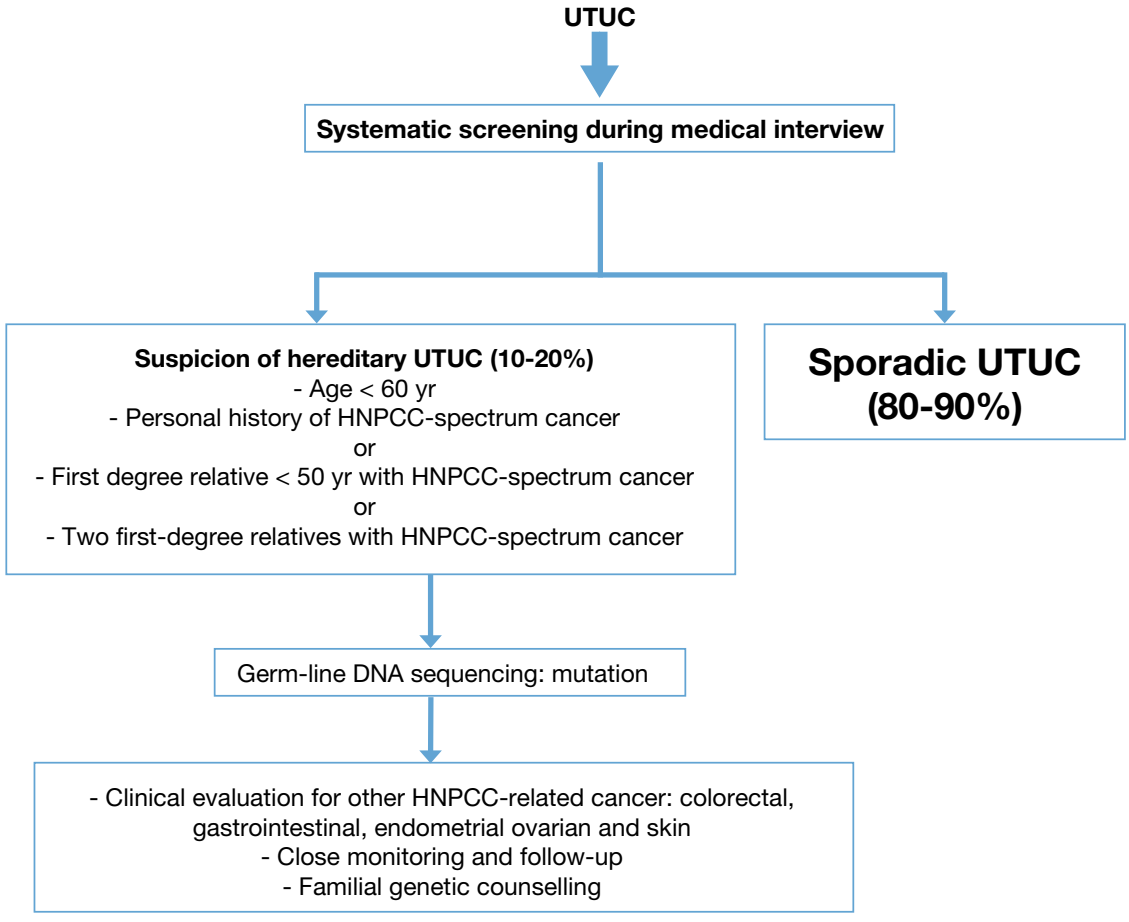
3.1 Epidemiology

Urothelial carcinomas (UCs) are the fourth most common tumours [2]. 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 [3]. However, UTUCs are uncommon and account for only 5-10% of UCs [2, 4], with an estimated annual incidence in Western countries of ~2 cases per 100,000 inhabitants. Pyelocaliceal tumours are about twice as common as ureteral tumours. In 17% of cases, concurrent bladder cancer is present [5]. Recurrence in the bladder occurs in 22-47% of UTUC patients [6-8], compared with 2-6% in the contralateral upper tract [9, 10].

Sixty percent 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 during interview (Figure 3.1) [16]. Patients should undergo DNA sequencing to identify hereditary cancers misclassified as sporadic [15, 17].

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



HNPCC = hereditary non-polyposis colorectal carcinoma.

3.2 Risk factors

Many environmental factors contribute to UTUC development [18, 19]. Tobacco exposure increases the relative risk from 2.5 to 7 [18, 19]. Historically, UTUC 'amino tumours' were related to occupational exposure to carcinogenic aromatic amines, including benzidine and β-naphthalene - both of which have been banned since the 1960s in most industrialised countries.

Upper tract urothelial carcinoma is mostly secondary to an amino tumour of the bladder. 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, 20]. Upper urinary tract 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 d-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, who present with UTUC [19, 21, 22].

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, 22]. There is a possible association of UTUC with blackfoot disease and arsenic exposure in drinking water in this population [19, 22, 23].

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. UTUC may share some risk factors or molecular disruption pathways with bladder urothelial carcinoma. Only two UTUC-specific polymorphisms have been reported [24, 25].

3.2 Histology and classification

*3.2.1 **Histological types***

There are morphological variants of UTUC that are more often observed in urothelial kidney tumours. These variants always correspond to high-grade tumours that are associated with one of the following [26]: micropapillary, clear cell, neuroendocrine or lymphoepithelial variants [27, 28]. Collecting-duct carcinoma can have similar characteristics to UTUC because of its common embryological origin [29].

UTUC with pure non-urothelial histology is an exception [30, 31] but variants are present in ~25% of cases [26, 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 is associated with chronic inflammatory and infectious diseases arising from urolithiasis [27, 28]. Other histological subtypes are adenocarcinoma (< 1%), small cell carcinoma, and sarcoma.

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.

Renal pelvic pT3 subclassification may discriminate between microscopic infiltration of the renal parenchyma (pT3a) and macroscopic infiltration or invasion of peripelvic adipose tissue. pT3a and pT3b have been suggested as a subclassification [26, 34, 35]. pT3b UTUC is more likely to have aggressive pathology and higher risk of recurrence [26, 34].

Table 4.1: TNM classification 2009 for upper tract urothelial carcinoma

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 recent 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].

5. DIAGNOSIS

5.1 Symptoms

Diagnosis of UTUC may be fortuitous or related to exploration of symptoms, which are generally limited [38]. The most common symptom is visible- or non-visible haematuria (70-80%) [39]. Flank pain occurs in 20-40% of cases, and a lumbar mass is present in 10-20% [40, 41]. Systemic symptoms (including anorexia, weight loss, malaise, fatigue, fever, night sweats, or cough) associated with UTUC should prompt more rigorous metastatic evaluation [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 high-risk patients [39]. The sensitivity of CTU for UTUC is 0.67-1.0 and the specificity is 0.93-0.99 [42-49].

Computed tomography urography acquires at least one image series during the excretory phase, usually 10-15 min, following administration of intravenous contrast medium [50). Rapid acquisition of thin sections allows for 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 upon imaging of UTUC 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 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 highly 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 detect upper urinary tract tumours [43, 60). Urinary cytology of the renal cavities and ureteral lumina is preferable before application of contrast agent for retrograde ureteropyelography, because it 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. 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 [61, 62]. FISH appears to have a limited value for surveillance of UTUCs [61, 62].

*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 [63]. Undergrading may occur from diagnostic biopsy, making intensive follow-up necessary if renal-sparing treatment is selected [64]. Ureteroscopy also facilitates selective ureteral sampling for cytology *in situ* [60, 65, 66].

Flexible ureteroscopy is especially useful for diagnostic uncertainty, when conservative treatment is considered, or in patients with a solitary kidney. Ureteroscopy and biopsy should be performed in preoperative assessment of UTUC. Combining ureteroscopic biopsy grade, imaging findings such as hydronephrosis, and urinary cytology, may help decide between radical nephroureterectomy (RNU) and endoscopic treatment [65, 67].

Technical developments in flexible ureteroscopes and the use of novel imaging techniques improve visualisation and diagnosis of flat lesions. Narrow-band imaging is the most promising technique but results are preliminary [67, 68]. Table 5.1 lists the recommendations for diagnosis.

Table 5.1: Diagnostic guidelines for upper tract urothelial carcinoma

Recommendations	GR
Urinary cytology should be performed as part of a standard diagnostic work-up.	A
A cystoscopy should be done to rule out concomitant bladder tumour.	A
CTU must be part of the diagnostic work-up.	A
Diagnostic ureteroscopy and biopsy should be performed, certainly in cases where additional information will impact treatment decisions.	C
Retrograde ureteropyelography is an optional tool for the detection of UTUC.	C

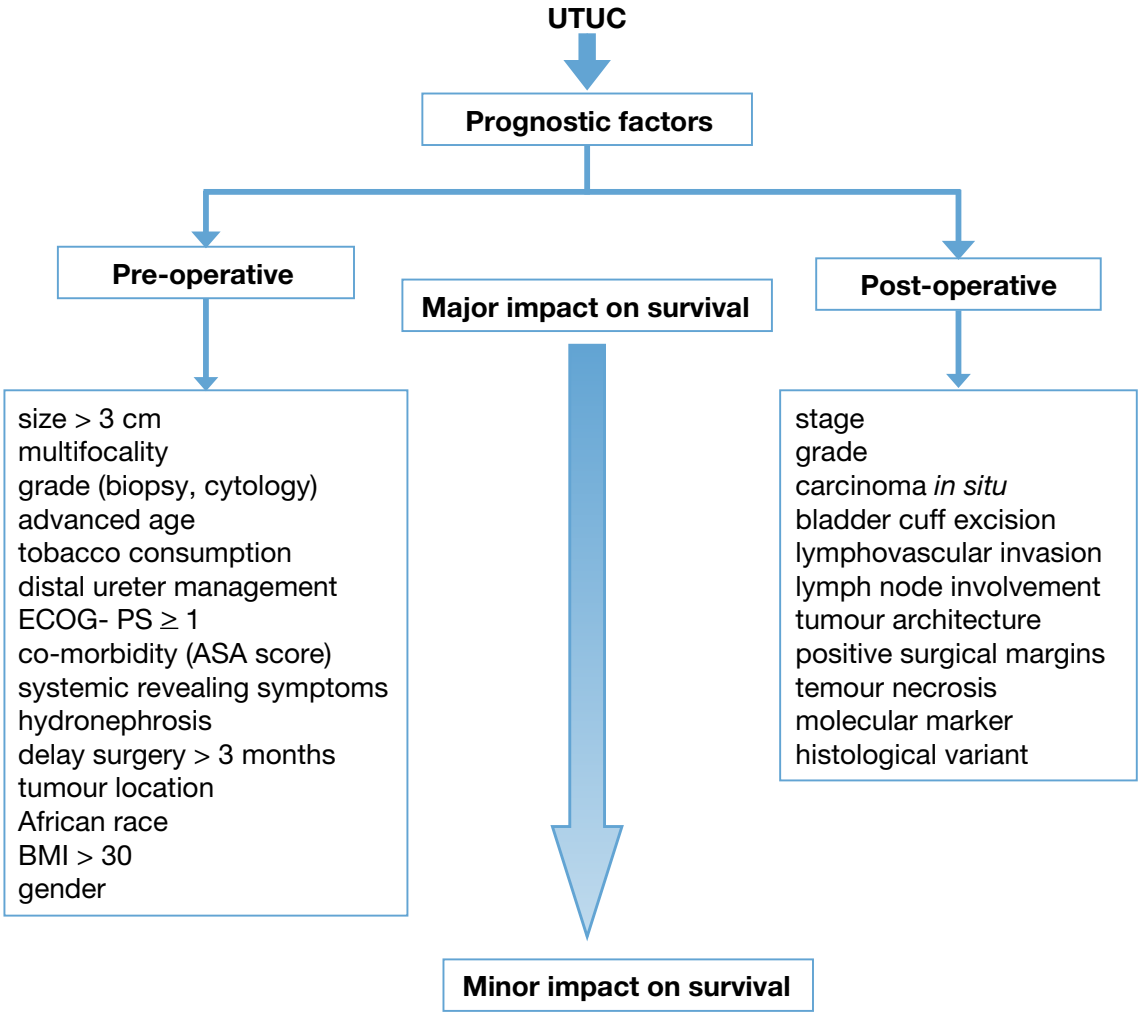
CTU = computed tomography urography; GR = grade of recommendation.

6. PROGNOSIS

6.1 Prognostic factors

Upper tract urothelial carcinomas that invade the muscle wall usually have poor prognosis. The 5-year specific survival is < 50% for pT2/pT3 and < 10% for pT4 [68-70). 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.

*6.1.1 **Preoperative factors***

6.1.1.1 Age and sex

Sex is no longer considered an independent prognostic factor that influences UTUC mortality [13, 70, 71]. Older age at the time of RNU is independently associated with decreased cancer-specific survival [70, 72] (LE: 3). Many elderly patients can be cured with RNU [72], suggesting that age alone is an inadequate indicator of outcome [72, 73]. Advanced age is linked with survival but it does not have to be considered as an absolute exclusion criterion for decision of treatment of potentially curable UTUC.

6.1.1.2 Ethnicity

One multicentre study did not show any difference between races [74] but population-based studies have indicated that African-American patients have worse outcomes compared to other racial groups [73] (LE: 3).

6.1.1.3 Tobacco consumption

Being a smoker at diagnosis increases the risk for poor oncological outcomes [75-77] and recurrence within the bladder [78] (LE: 3).

6.1.1.4 Tumour location

Initial location of the tumour within the upper urinary tract is a prognostic factor [79-81] (LE: 3). After adjustment for tumour stage, ureteral and multifocal tumours have a worse prognosis than renal pelvic tumours [70, 80-83].

6.1.1.5 Surgical waiting time

A delay between diagnosis and tumour removal may increase the risk of disease progression. The cut-off for

removal is controversial and ranges between 30 days and 3 months [84-87] (LE: 3).

6.1.1.6 Other

The American Society of Anesthesiologists (ASA) score also significantly correlates with cancer-specific survival after RNU [88] (LE: 3), but Eastern Cooperative Oncology Group (ECOG) performance status correlates only with overall survival [89]. Obesity and higher body mass index adversely affect cancer-specific outcomes in UTUCs [90) (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 [65, 70, 91, 92].

6.1.2.2 Lymph node involvement

Extranodal extension is a powerful predictor of clinical outcomes in UTUCs and positive lymph node metastases [93]. Lymph node dissection (LND) associated with RNU allows for optimal tumour staging [94, 95] (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 [96, 97]. Lymphovascular invasion status should be systematically included and specifically reported in the pathological reports of all RNU specimens [96, 98] (LE: 3).

6.1.2.4 Surgical margins

Positive 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 if it is T > 2 [99] (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 [100, 101] (LE: 3). The tissue architecture of UTUC is associated with prognosis after RNU. Sessile growth pattern is associated with the worst outcome [102, 103] (LE: 3). Concomitant CIS in organ-confined UTUC, and a history of bladder CIS are associated with a higher risk of recurrence and cancer-specific mortality [104-106] (LE: 3). Similar to lower tract UC, concomitant CIS is an independent predictor of worse outcomes in organ-confined disease [107].

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), and c-met protein (MET) [70, 108-112]. Microsatellite instability (MSI) is an independent molecular prognostic maker [113]. MSI can help detect germ-line 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.

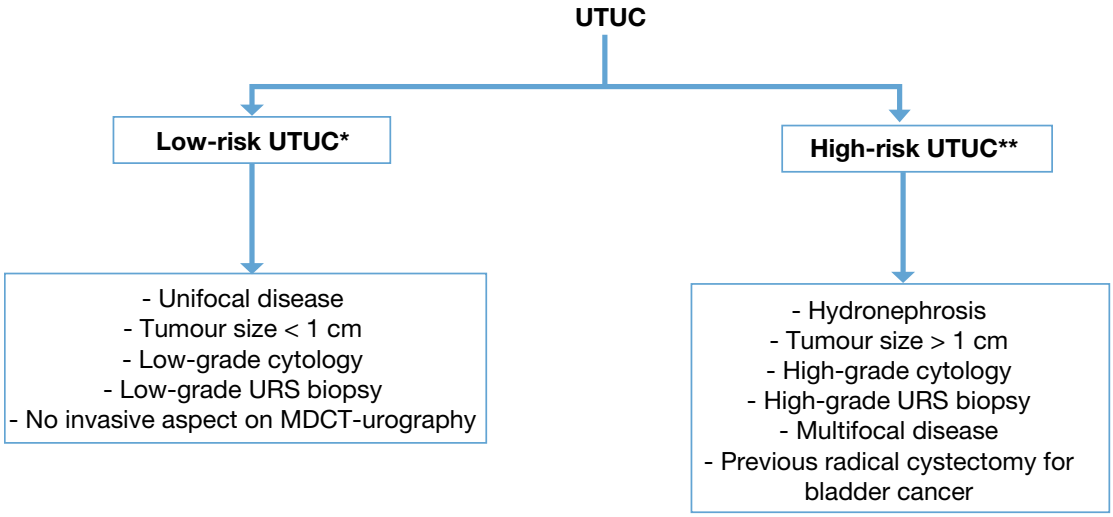
6.3 Predictive tools

Accurate predictive tools are rare for UTUC. There are two models in a preoperative setting: one for prediction LND of locally advanced cancer that could guide the extent of LND at the time of RNU [114]; and one for selection of non-organ-confined UTUC that is likely to benefit from nephroureterectomy [115]. Four nomograms predict survival rates postoperatively based on standard pathological features [116-119].

6.4 Risk stratification

As with NMIBC, it is necessary to 'risk stratify' UTUC before treatment to identify tumours that are more suitable for kidney-sparing treatment than radical extirpative surgery [120) (Figure 6.2).

Figure 6.2: Risk stratification of upper tract urothelial carcinoma



** All of these factors need to be present*

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

MDCT = multidetector-row computed tomography; URS = ureterorenoscopy.

7. DISEASE MANAGEMENT

7.1. Localised disease

*7.1.1 **Kidney-sparing surgery***

Conservative management of UTUC can be discussed in low-risk cases when the contralateral kidney is functional [121-123]. Kidney-sparing surgery for low-risk UTUC (Table 7.1) allows sparing the morbidity associated with open radical surgery, without compromising oncological outcomes and kidney function [124]. In addition, it can also be considered in all imperative cases (i.e.; renal insufficiency or solitary functional kidney) (LE: 3).

7.1.1.1 Ureteroscopy

Endoscopic ablation can be considered in highly selected cases and in the following situations [125, 126]:

- Laser generator [127] and pliers are available for biopsies [126, 128] (LE: 3);
- Flexible rather than rigid ureteroscope;
- The patient is informed of the need for closer, more stringent, surveillance;
- Complete tumour resection is strongly advocated.

However, there is a risk of understaging and undergrading with pure endoscopic management.

7.1.1.2 Percutaneous access

Percutaneous management can be considered for low-grade or non-invasive UTUCs in the renal cavities [126, 129, 130) (LE: 3). This may be offered for low-grade 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 enhanced materials and advances in distal-tip deflection of recent ureteroscopes [126, 129, 130).

7.1.1.3 Segmental resection

Segmental ureteral resection with wide margins provides adequate pathological specimens for staging and grading, while preserving the ipsilateral kidney.

- Ureteroureterostomy is indicated for non-invasive, low-grade tumours of the proximal- or mid-ureter that cannot be removed completely endoscopically, and for high-grade or invasive tumours when renal-sparing surgery for renal function preservation is a goal.
- High-grade tumours of the proximal- or mid-ureter should undergo RNU with bladder cuff excision. Complete distal ureterectomy +/- neocystostomy are indicated for non-invasive, low-grade tumours

in the distal ureter that cannot be removed completely endoscopically, and for high-grade, locally-invasive tumours [131-133] (LE: 3).
- Segmental resection of the iliac and lumbar ureter is associated with greater failure than for the distal pelvic ureter [131-133].
- Open resection of tumours of the renal pelvis or calices has almost disappeared.
- Resection of pyelocaliceal tumours is technically difficult and has higher recurrence than ureteral tumours.

Table 7.1: Guidelines for kidney-sparing management of low-risk upper tract urothelial carcinoma

Indications for endourological management	**GR**
Unifocal tumour.	B
Tumour < 1 cm.	B
Low-grade tumour.	B
No evidence of infiltrative lesion on CTU.	B
Understanding of close follow-up.	B
Techniques used according to location:	
• Laser should be used for endoscopic treatment.	C
• Flexible is preferable to rigid ureteroscopy: renal pelvis, distal-, mid- and proximal ureter.	C
• Percutaneous approach remains an option for low grade tumours not accessible by ureteroscopic approach.	C
Surgical open approach	
Renal pelvis or calyces: Partial pyelectomy or partial nephrectomy is seldom indicated.	C
Ureter - Mid & proximal: Ureteroureterostomy is indicated for tumours that cannot be removed completely endoscopically.	C
Ureter - Distal: Complete distal ureterectomy and neocystostomy are indicated for tumours in the distal ureter that cannot be removed completely endoscopically.	C

CTU = computed tomography urography; GR = grade of recommendation.

7.1.1.4 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 conservative treatment of UTUC or for treatment of CIS [134] (LE: 3). Retrograde instillation through a ureteric stent is also used but it can be dangerous due to possible ureteric obstruction and consecutive pyelovenous influx during instillation/perfusion. The reflux obtained from a double-J stent has been used [135], but is not advisable since it often does not reach the renal pelvis.

*7.1.2 **Radical nephroureterectomy***

Open RNU with bladder cuff excision is the standard for high-risk UTUC, regardless of tumour location [12] (LE: 3). Radical nephroureterectomy must comply with oncological principles, which consist of preventing tumour seeding by avoiding 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. Removal of the distal ureter and bladder cuff is beneficial after RNU [121, 136, 137]. Regardless of the technique, the surgeon must be confident that the bladder is closed appropriately.

Several techniques have been considered to simplify distal ureter resection, including pluck technique, stripping, transurethral resection of the intramural ureter, and intussusception [9, 137, 138]. Except for ureteral stripping, none of these techniques is inferior to bladder cuff excision [72-74, 80) (LE: 3). Endoscopy is associated with a higher risk of subsequent bladder recurrence [139, 140).

7.1.2.1 Laparoscopic radical nephroureterectomy

Retroperitoneal metastatic dissemination and dissemination along the trocar pathway following manipulation of large tumours in a pneumoperitoneal environment have been reported in only few cases [141, 142].

Several precautions are needed with pneumoperitoneum because it may increase tumour spillage:
- Entering the urinary tract should be avoided;
- Direct contact between instruments and tumour should be avoided;

- Laparoscopic RNU must take place in a closed system. Morcellation of the tumour should be avoided and an endobag is necessary 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.

Safety of laparoscopic RNU has been demonstrated. There is a tendency towards equivalent oncological outcomes after laparoscopic or open RNU [142-148] (LE: 3).

Only one prospective randomised study has shown that laparoscopic RNU is not inferior to open RNU for non-invasive UTUC [149] (LE: 2). Oncological outcomes after RNU have not changed significantly over the past three decades despite staging and surgical refinements [150) (LE: 3).

7.1.2 2 Lymph node dissection

Anatomical sites of LND have not been clearly defined. The LND template is likely to have a greater impact on patient survival than the number of lymph nodes removed [127].

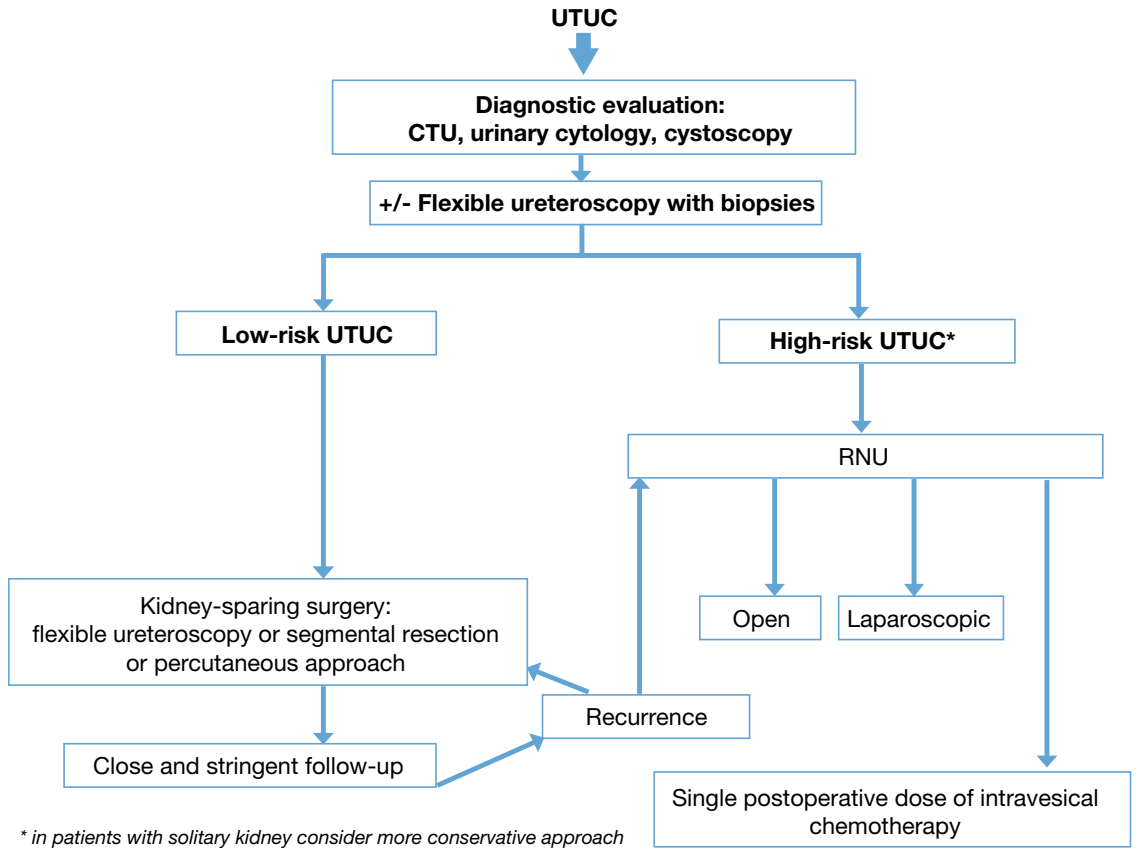
Lymph node dissection appears to be unnecessary in cases of TaT1 UTUC because lymph node retrieval is reported in only 2.2% of T1 versus 16% of pT2-4 tumours [95]. An increase in the probability of lymph-node-positive disease is related to pT classification [95]. However, it is likely that the true rate of node-positive disease has been under-reported because these data are retrospective.

It is not possible to standardise indication or extent of LND. Lymph node dissection 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) [94, 95, 127].

7.1.2.3 Chemotherapy

One prospective randomised study has demonstrated that a single postoperative dose of intravesical mitomycin on the day of catheter removal reduces the risk of bladder tumour within the first year post-RNU [151] (LE: 2). This therapeutic strategy was confirmed in another prospective trial with pirarubicin [152] and in a meta-analysis [153]. Management is outlined in Figure 7.1.

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



CTU = computed tomography urography; RNU = radical nephroureterectomy.

Table 7.2: Guidelines for radical nephroureterectomy in upper tract urothelial carcinoma

Indications for RNU	GR
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
Techniques for RNU	
Open and laparoscopic access has equivalent efficacy in T1-T2/N0 tumours.	B
Bladder cuff removal is imperative.	A
Several techniques for bladder cuff excision are acceptable, except stripping.	C
Lymphadenectomy is recommended for invasive UTUC.	C
Postoperative instillation is recommended after RNU to avoid bladder recurrence.	B

GR = grade of recommendation; RNU = radical nephroureterectomy.

7.2 Advanced disease

*7.2.1 **Radical nephroureterectomy***

There are no benefits of RNU in metastatic disease, although it can be considered as palliative [12, 95] (LE: 3).

*7.2.2 **Systemic chemotherapy***

Upper tract urothelial carcinomas are urothelial tumours; therefore, platinum-based chemotherapy is expected to have similar efficacy as in bladder cancer. However, there are currently insufficient data for recommendations.

There are several platinum-based regimens [154], but the risk of impaired postoperative function means that neoadjuvant chemotherapy is only optional. Not all patients can receive chemotherapy because of comorbidity and impaired renal function after radical surgery. Chemotherapy-related toxicity, particularly nephrotoxicity from platinum derivatives, may significantly reduce survival in patients with postoperative renal dysfunction [155, 156].

There were no adverse effects of neoadjuvant chemotherapy for UTUCs in the only study published to date [157], although survival data need to mature and longer follow-up is awaited.

Adjuvant chemotherapy can achieve a recurrence-free rate of ≤ 50% [158, 159]. After a recent comprehensive search of studies examining the role of chemotherapy for UTUC, there appears to be an overall survival and disease-free survival benefit for cisplatin-based adjuvant chemotherapy [160) (LE: 3). However, it is challenging to make a definitive statement until further evidence from an ongoing prospective trial is available [161].

*7.2.3 **Radiotherapy***

Radiotherapy is no longer relevant, either alone or as an adjunct to chemotherapy [162, 163] (LE: 3).

8. FOLLOW-UP

The risk of recurrence and death evolves over the follow-up after surgery [164]. Stringent follow-up (Table 6) is mandatory to detect metachronous bladder tumours, 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. The rate of bladder recurrence after treatment of primary UTUC is 22-47% [6, 8].

Surveillance regimens are based on cystoscopy and urinary cytology for ≥ 5 years [6-8]. Bladder recurrence should not be considered as distant recurrence. When conservative treatment is performed, the ipsilateral upper urinary tract requires careful follow-up due to the high risk of recurrence [122, 128, 165]. Despite endourological improvements, follow-up after conservative therapy is difficult, and frequent, repeated endoscopic procedures are necessary.

Table 8.1: Guidelines for follow-up of upper tract urothelial carcinoma patients after initial treatment

After RNU, ≥ 5 years	**GR**
Non-invasive tumour	
• Cystoscopy/urinary cytology at 3 months and then yearly.	C
• CT every year	C
Invasive tumour	
• Cystoscopy/urinary cytology at 3 months and then yearly.	C
• CT urography every 6 months over 2 years and then yearly.	C
After conservative management, ≥ 5 years	
• Urinary cytology and CTU at 3 and 6 months, and then yearly.	C
• Cystoscopy, ureteroscopy and cytology *in situ* at 3 and 6 months, and then every 6 months over 2 years, and then yearly.	C

CTU = computed tomography urography; GR = grade of recommendation; 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://www.uroweb.org/guidelines/. This guidelines document was developed with the financial support of the European Association of Urology. No external sources of funding and support have been involved. The EAU is a non-profit organization, and funding is limited to administrative assistance and travel and meeting expenses. No honoraria or other reimbursements have been provided.