EAU Guidelines on

Upper Urinary Tract Urothelial Carcinoma

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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 as an app for iOS and Android 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, the most recent scientific summary was published in 2017 [4]. 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 2018 EAU Guidelines on UTUC present a limited update of the 2017 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 2018 print:

- Figure 6.2 - Risk stratification of upper urinary tract urothelial carcinoma, tumour size cut off for high-risk UTUC has been changed to > 2 cm;
- Section 6.6 - Summary of evidence and guidelines for prognosis – recommendation 'Use the America Society of Anesthesiologists score to assess cancer-specific survival' – was taken out;
- Section 7.1.4.3 - Summary of evidence and recommendations for radical nephroureterectomy.

Recommendations	Strength rating
Perform radical nephroureterectomy in patients with high-risk tumours.	Strong
Technical steps of radical nephroureterectomy:	
Offer a post-operative bladder instillation of chemotherapy to lower the intravesical recurrence rate.	Strong

- Section 8.1: Summary of evidence and follow-up of UTUC

Recommendations	Strength rating
After radical nephroureterectomy:	
Low-risk tumour	
Perform cystoscopy at three months. If negative, perform subsequent cystoscopy nine months later and then yearly, for five years.	Weak

High-risk tumours	
Perform cystoscopy and urinary cytology at three months. If negative, repeat subsequent cystoscopy and cytology every three months for a period of two years, and every six months thereafter until five years, and then yearly.	Weak
Perform computed tomography urography every six months for two years, and then yearly.	Weak
After kidney-sparing management:	
Low-risk tumours	
Perform cystoscopy and computed tomography urography at three and six months, and then yearly for five years.	Weak
Perform ureteroscopy at three months.	Weak
High-risk tumours	
Perform cystoscopy, urinary cytology and computed tomography urography at three and six months, and then yearly.	Weak
Perform ureteroscopy and urinary cytology *in situ* at three and six months.	Weak

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 2018 UTUC Guidelines, new and relevant evidence has been identified, collated and appraised through a structured assessment of the literature. The search was restricted to articles published between January 1st 2016 and July 12th 2017. 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 510 unique records were identified, retrieved and screened for relevance. 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 publications identified were mainly retrospective, including some large multicentre studies. Owing to the scarcity of randomised data, articles were selected based on the following criteria: evolution of concepts, intermediate- and long-term clinical outcomes, study quality, and relevance. Older studies were only included if they were historically relevant. A detailed search strategy is available online: http://uroweb.org/guideline/upper-urinary-tract-urothelial-cell-carcinoma/?type=appendicespublications.

For Chapters 3-6 (Epidemiology, Aetiology and Pathology, Staging and Classification systems, Diagnosis and Prognosis) references used in this text are assessed according to their level of evidence (LE) based on the 2009 Oxford Centre for Evidence-Based Medicine (CEBM) Levels of Evidence [5]. For the Disease Management and Follow-up chapters (Chapters 7 and 8) a system modified from the 2009 CEBM levels of evidence has been used [5].

For the 2018 edition of the EAU Guidelines the Guidelines Office have transitioned to a modified GRADE methodology across all 20 guidelines [6, 7]. For each recommendation within the guidelines there is an accompanying online strength rating form which addresses a number of key elements namely:

1. the magnitude of the effect (individual or combined effects);
2. the certainty of the results (precision, consistency, heterogeneity and other statistical or study related factors);
3. the balance between desirable and undesirable outcomes;
4. the impact of patient values and preferences on the intervention;
5. the certainty of those patient values and preferences.

These key elements are the basis which panels use to define the strength rating of each recommendation. The strength of each recommendation is represented by the words ‘strong’ or ‘weak’ [6, 7]. The strength of each recommendation is determined by the balance between desirable and undesirable consequences of alternative management strategies, the quality of the evidence (including certainty of estimates), and nature and variability of patient values and preferences. The strength rating forms will be available online.

Additional information can be found in the general Methodology section of this print, and online at the EAU website; http://www.uroweb.org/guideline/.

Specific sections were updated by way of systematic reviews based on topics or questions prioritised by the Guideline Panel. These reviews were performed using standard Cochrane systematic review methodology; http://www.cochranelibrary.com/about/about-cochrane-systematic-reviews.html.

The results of two systematic reviews [8, 9] have been included in the 2018 UTUC Guidelines in sections:

- 7.1.4.2 *Laparoscopic radical nephroureterectomy* [8]
- 7.1.5 *Lymph node dissection* [9]

A list of Associations endorsing the EAU Guidelines can also be viewed online at the above address.

2.2 Review

The systematic review publications have been peer-reviewed prior to publications. The UTUC Guidelines have been peer-reviewed prior to publication in 2016.

3. EPIDEMIOLOGY, AETIOLOGY AND PATHOLOGY

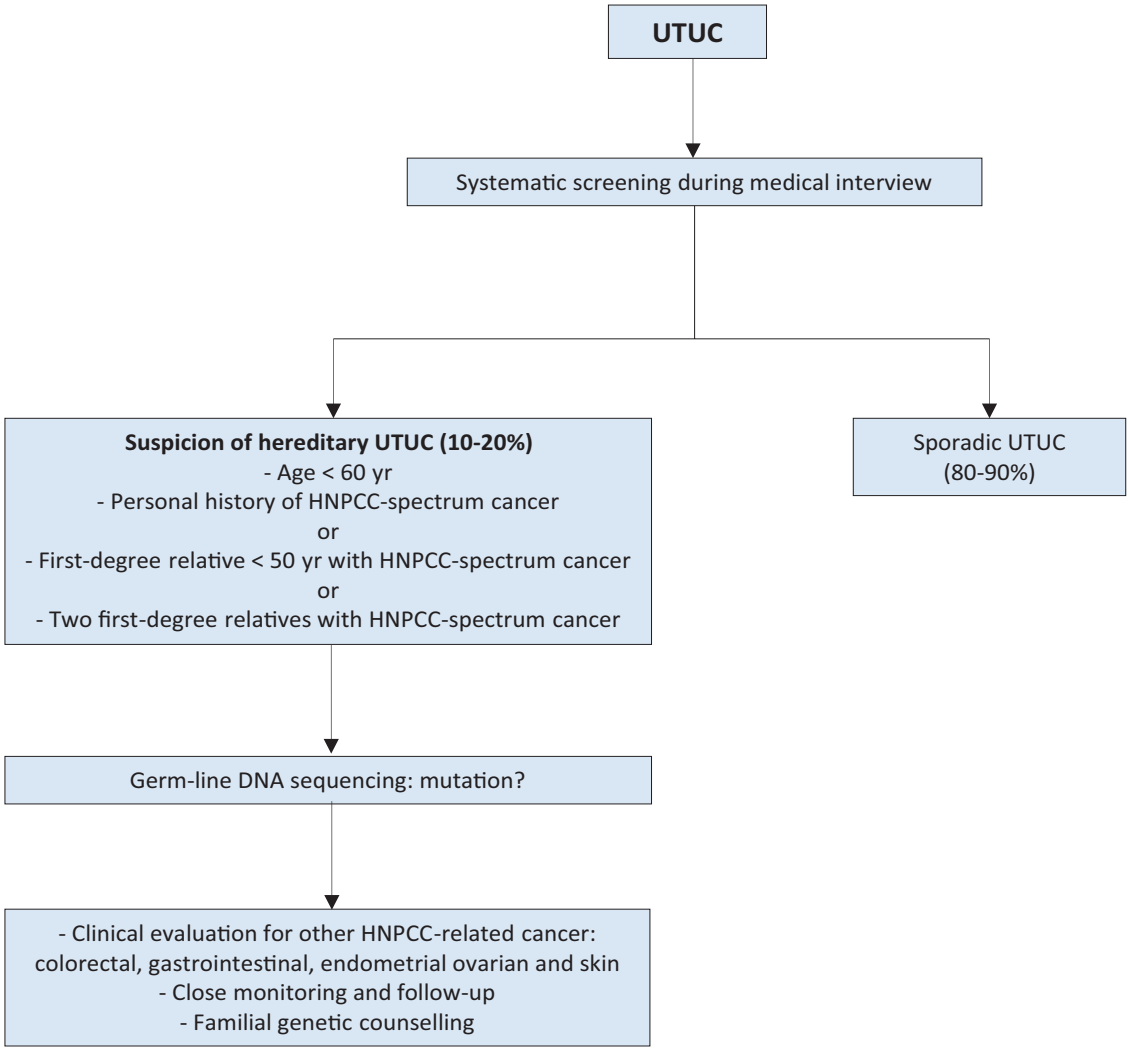
3.1 Epidemiology

Urothelial carcinomas are the fourth most common tumours [10]. They can be located in the lower (bladder and urethra) or the upper (pyelocaliceal cavities and ureter) urinary tract. Bladder tumours account for 90–95% of UCs and are the most common urinary tract malignancy [1]. Urothelial carcinomas of the upper urinary tract are uncommon and account for only 5–10% of UCs [10, 11] with an estimated annual incidence in Western countries of almost two cases per 100,000 inhabitants. This rate has risen in the past few decades as a result of improved detection and improved bladder cancer survival [12]. Pyelocaliceal tumours are approximately twice as common as ureteral tumours whilst multifocal tumours are found in 10-20%. The presence of concomitant carcinoma *in situ* of the upper tract is between 11 and 36% [12]. In 17% of cases, concurrent bladder cancer is present [13] whilst a prior history of bladder cancer is found in 41% of American men but in only 4% of Chinese men [14]. This, along with genetic and epigenetic factors, may explain why Asian patients present with more advanced and higher grade disease compared to other ethnic groups [12]. Following treatment, recurrence in the bladder occurs in 22–47% of UTUC patients [15] compared with 2-6% in the contralateral upper tract [16].

At diagnosis, 60% of UTUCs are invasive at diagnosis compared with 15–25% of bladder tumours [17] and 7% have metastasised [12]. UTUCs have a peak incidence in individuals aged 70–90 years and are three times more common in men [18].

Familial/hereditary UTUCs are linked to hereditary nonpolyposis colorectal carcinoma [19], and these patients can be screened during a short interview (Figure 1) [20]. Patients identified at high risk for hereditary nonpolyposis colorectal carcinoma (HNPCC) syndrome should undergo DNA sequencing for patient and family counselling [19, 21].

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



HNPCC = hereditary nonpolyposis colorectal carcinoma; UTUC = upper urinary tract urothelial carcinoma.

3.2 Risk factors

Many environmental factors contribute to the development of UTUC [22]. Tobacco exposure increases the relative risk from 2.5 to 7 [23].

Historically, UTUC "amino tumours" were related to occupational exposure to carcinogenic aromatic amines including benzidine and b-naphthalene, both of which have been banned since the 1960s in most industrialised countries.

The average duration of exposure needed to develop UTUC is 7 years, with a latency of up to 20 years following termination of exposure.

Several studies have demonstrated the carcinogenic potential of aristolochic acid contained in Aristolochia fangchi and clematis plants. The aristolochic acid–derivative d-aristolactam is associated with a specific mutation in the *p53* gene at codon 139 that occurs mainly in patients with nephropathy due to Chinese herbs or Balkan endemic nephropathy [22, 24]. Although the incidence of Balkan endemic nephropathy is also declining, aristolochic acid plays a key role in the pathophysiology of this nephropathy. There is a high incidence of UTUC in Taiwan, especially on the southwest coast, which represents 20–25% of UCs in the region [22]. There is a possible association between UTUC, blackfoot disease, and arsenic exposure in drinking water in this population [25] as well as aristolochic acid in Chinese herbs [22, 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 that introduces variability in the inter-individual susceptibility to the risk factors previously mentioned. UTUC may share some risk factors and molecular pathways with bladder UC. So far, two UTUC-specific polymorphisms have been reported [27].

3.3 Histology and classification

*3.3.1 **Histological types***

UTUC with pure non-urothelial histology is rare [28, 29] but variants are present in approximately 25% of cases [30, 31]. These variants correspond to high-grade tumours with worse prognosis compared with pure UC [32]. Squamous cell carcinoma of the UUT represents < 10% of pyelocaliceal tumours and is even rarer within the ureter. Squamous cell carcinoma of the urinary tract is often assumed to be associated with chronic inflammatory diseases and infections arising from urolithiasis [33, 34]. Other variants, although rare, include: sarcomatoid and urothelial carcinomas with inverted growth [32]. Collecting duct carcinoma can have similar characteristics to UTUC due to its common embryological origin [35]. They are, however, considered as kidney cancers and not UTUC.

4. STAGING AND CLASSIFICATION SYSTEMS

4.1 Classification

The classification and morphology of UTUC and bladder carcinoma are similar [1]. It is possible to distinguish between non-invasive papillary tumours (papillary urothelial tumours of low malignant potential and low- and high-grade papillary UC) [36], flat lesions (carcinoma *in situ* [CIS]), and invasive carcinoma. As in bladder tumours, non-urothelial differentiation (i.e., histologic variants) confers an adverse risk factor.

4.2 Tumour Node Metastasis staging

The tumour, node, metastasis (TNM) classification is shown in Table 1 [37]. The regional lymph nodes are the hilar and retroperitoneal nodes and, for the mid and distal ureter, the intrapelvine 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 (pT3b) [30, 38, 39]. pT3b UTUC has a higher risk of disease recurrence after radical nephroureterectomy (RNU) [30, 38].

Table 1: TNM classification 2017 for upper tract urothelial cell carcinoma [37]

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

TNM = Tumour, Node, Metastasis (classification).

4.3 Tumour grade

Until 2004, the 1973 World Health Organisation (WHO) classification was used for tumour grading and distinguished grades G1–G3 [40]. The 2004/2016 WHO classification considers histological data to distinguish between non-invasive tumours: papillary urothelial neoplasia of low malignant potential, and low- and high-grade carcinomas (low grade vs. high grade). The current guidelines are based on the 2004/2016 WHO classification [40, 41].

5. DIAGNOSIS

5.1 Symptoms

The diagnosis of UTUC may be incidental or related to the evaluation of symptoms that are generally limited. The most common symptom is visible or nonvisible haematuria (70–80%) [42, 43]. Flank pain occurs in approximately 20% of cases, and a lumbar mass is present in approximately 10% [44, 45]. Systemic symptoms (including anorexia, weight loss, malaise, fatigue, fever, night sweats, or cough) associated with UTUC should prompt more rigorous metastatic evaluation; they confer a worse prognosis [44, 45].

5.2 Imaging

*5.2.1 **Computed tomography urography***

Computed tomography (CT) urography has the highest diagnostic accuracy of the available imaging techniques [45]. The sensitivity of CT urography for UTUC is 0.67–1.0 and specificity is 0.93–0.99 [46].

Rapid acquisition of thin sections allows high-resolution isotropic images that can be viewed in multiple planes to assist with diagnosis without loss of resolution. Epithelial "flat lesions" without mass effect or urothelial thickening are generally not visible with CT.

The secondary sign of hydronephrosis is associated with advanced disease and poor oncological outcome [47, 48]. The presence of enlarged lymph nodes is highly predictive of metastases in UTUC [49].

*5.2.2 **Magnetic resonance urography***

Magnetic resonance (MR) urography is indicated in patients who cannot undergo CT urography, usually when radiation or iodinated contrast media are contraindicated [50]. The sensitivity of MR urography is 0.75 after contrast injection for tumours < 2 cm [50]. The use of MR urography 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. CT urography is generally preferred to MR urography for diagnosing and staging UTUC.

5.3 Cystoscopy and urinary cytology

Abnormal cytology findings are suggestive of UTUC when bladder cystoscopy is normal, provided no CIS in the bladder or prostatic urethra has been detected [1, 51, 52]. Cytology is less sensitive for UTUC than bladder tumours and should be performed *in situ* in the renal cavities [53]. Retrograde ureteropyelography remains an option to detect UTUCs [46, 54, 55]. Urinary cytology of the renal cavities and ureteral lumina is preferred before application of a contrast agent for retrograde ureteropyelography because it may cause deterioration of cytological specimens [47, 55].

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 kidney-sparing therapy for UTUCs [56, 57]. Therefore, FISH has limited value in the surveillance of UTUCs [56, 57].

5.4 Diagnostic ureteroscopy

Flexible ureteroscopy (URS) is used to visualise the ureter, renal pelvis and collecting system and, for biopsy of suspicious lesions. Ureteroscopic biopsies can determine tumour grade in 90% of cases with a low false-negative rate, regardless of sample size [58]. Undergrading may occur following diagnostic biopsy, making intensive follow-up necessary if kidney-sparing treatment is chosen [59]. Ureteroscopy also facilitates selective ureteral sampling for cytology *in situ* [55, 60, 61]. Stage assessment using ureteroscopic biopsy is notoriously difficult.

Flexible ureteroscopy is particularly useful in 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 RNU and kidney-sparing therapy [61, 62]. However, recent studies suggest a higher rate of intravesical recurrence in patients (particularly in case of renal pelvic tumour) who underwent URS before RNU [63, 64].

Technical developments in flexible ureteroscopes and the use of novel imaging techniques improve visualisation and diagnosis of flat lesions [65]. Narrow-band imaging is a promising technique, but results are preliminary [62, 66, 67]. Optical coherence tomography and confocal laser endomicroscopy (Cellvizio©) have been used *in vivo* to evaluate tumour grade and/or for staging purposes, with a promising correlation with definitive histology in high-grade UTUC [68, 69]. Recommendations are listed in Section 5.5.

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

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

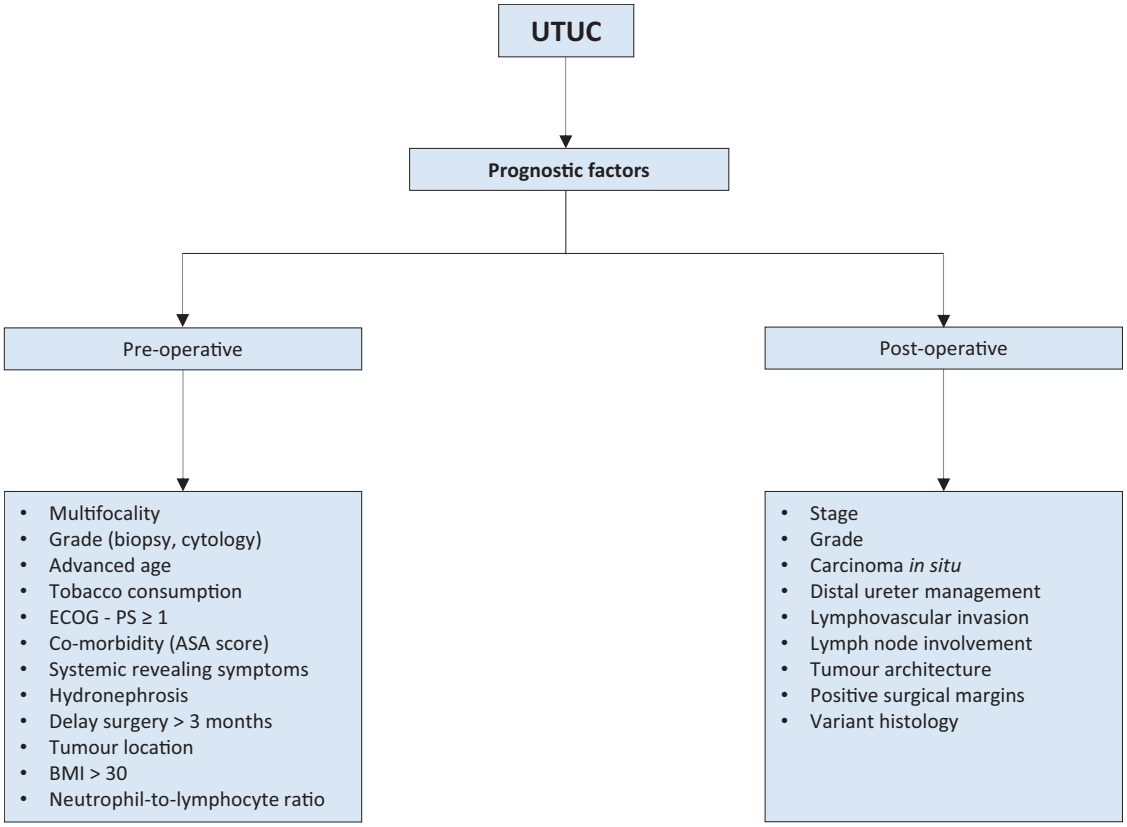
Recommendations	Strength rating
Perform a cystoscopy to rule out concomitant bladder tumour.	Strong
Perform a computed tomography urography for upper tract evaluation and for staging.	Strong
Use diagnostic ureteroscopy and biopsy only in cases where additional information will impact treatment decisions.	Strong

6. PROGNOSIS

6.1 Prognostic factors

UTUCs that invade the muscle wall usually have a very poor prognosis. The 5-year specific survival is < 50% for pT2/pT3 and < 10% for pT4 [66, 70, 71]. The main prognostic factors are briefly listed here. Figure 2 shows an exhaustive list.

Figure 6.1: Upper urinary tract urothelial cell carcinoma: prognostic factors



ASA = American Society of Anesthesiologists; BMI = body mass index; ECOG PS = Eastern Cooperative Oncology Group performance status performance score; UTUC = upper urinary tract urothelial cell carcinoma.

6.2 Pre-operative factors

*6.2.1 **Age and gender***

Age is one of the most important demographic predictors of survival in UTUC [72]. Older age at the time of RNU is independently associated with decreased cancer-specific survival [39, 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. Gender is no longer considered an independent prognostic factor influencing UTUC mortality [18, 71, 75].

*6.2.2 **Ethnicity***

One multicentre study did not show any difference in outcome between races [76], but population-based studies have indicated that African-American patients have worse outcomes than other ethnicities (LE: 3). Another study has underlined differences between China and US patients at presentation (risk factor, disease characteristics and predictors of adverse oncologic outcomes) [14].

*6.2.3 **Tobacco consumption***

Being a smoker at diagnosis increases the risk for disease recurrence and mortality after RNU [77, 78] and recurrence within the bladder [79] (LE: 3). There is a close relationship between tobacco consumption and prognosis; smoking cessation improves cancer control.

*6.2.4 **Tumour location***

Initial location of the UTUC is a prognostic factor in some studies [80, 81] (LE: 3). After adjustment for the effect of tumour stage, patients with ureteral and/or multifocal tumours seem to have a worse prognosis than renal pelvic tumours [71, 80-83].

*6.2.5 **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, when possible [84-86, 87] (LE: 3).

*6.2.6 **Other***

The American Society of Anesthesiologists score also significantly correlates with cancer-specific survival after RNU [88] (LE: 3), as well as poor performance status [89, 89]. Obesity and higher body mass index adversely affect cancer-specific outcomes in UTUCs [90] (LE: 3). The pre-treatment-derived neutrophil-lymphocyte ratio also correlates with higher cancer-specific mortality [91].

6.3 Post-operative factors

*6.3.1 **Tumour stage and grade***

The primary recognised prognostic factors are tumour stage and grade [61, 71, 72, 92, 93].

*6.3.2 **Lymph node involvement***

Lymph node metastases and extranodal extension are powerful predictors of survival outcomes in UTUC [94]. Lymph node dissection (LND) performed at the time of RNU allows for optimal tumour staging [95, 96] (LE: 3). Its curative role remains debated.

*6.3.3 **Lymphovascular invasion***

Lymphovascular invasion is present in approximately 20% of UTUCs and is an independent predictor of survival [97, 98]. Lymphovascular invasion status should be specifically reported in the pathological reports of all UTUC specimens [97, 99] (LE: 3).

*6.3.4 **Surgical margins***

Positive soft tissue surgical margin after RNU is a significant factor for developing disease recurrence. Pathologists should look for and report positive margins at the level of ureteral transection, bladder cuff, and around the tumour if T > 2 [100] (LE: 3).

*6.3.5 **Pathological factors***

Extensive tumour necrosis (> 10% of the tumour area) is an independent prognostic predictor in patients who undergo RNU [101, 102] (LE: 3). The architecture of UTUC is also a strong prognosticator with sessile growth pattern being associated with worse outcome [103, 104] (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 [105, 106] (LE: 3).

6.4 Molecular markers

Several studies have investigated the prognostic impact of molecular markers related to cell adhesion (E-cadherin [107] and CD24), cell differentiation (Snail and human epidermal growth factor receptor *HER-2* [108]), angiogenesis (hypoxia inducible factor 1α and metalloproteinases), cell proliferation (Ki-67), epithelial-mesenchymal transition (Snail), mitosis (Aurora A), apoptosis (*Bcl-2* and survivin), vascular invasion (RON), and c-met protein (MET) [71, 109]. Microsatellite instability (MSI) is an independent molecular prognostic marker [110]. Microsatellite instability typing can help detect germline mutations and hereditary cancers [19]. Interestingly, there is a prognostic value of PD-1 and PDL-1 expression in patients with high grade UTUC [111].

Because of the rarity of UTUC, the main limitations of molecular studies are their retrospective design and, for most studies, small sample size. None of the markers have yet fulfilled the criteria necessary to support their introduction in daily clinical decision making.

6.5 Predictive tools

Accurate predictive tools are rare for UTUC. There are two models in the pre-operative setting: one for predicting LND of locally advanced cancer that could guide the decision to perform, or not, an LND as well as the extent of LND at the time of RNU [112], and one for the selection of non–organ-confined UTUC that is likely to benefit from RNU [113]. Five nomograms are available predicting survival rates post-operatively, based on standard pathological features [114-118], one of which is based on only four variables with a higher prognostic accuracy and risk stratification [119].

*6.5.1 **Bladder recurrence***

A recent meta-analysis of available data has identified significant predictors of bladder recurrence after RNU [120] (LE: 3). Three categories of predictors of increased risk for bladder recurrence were identified:

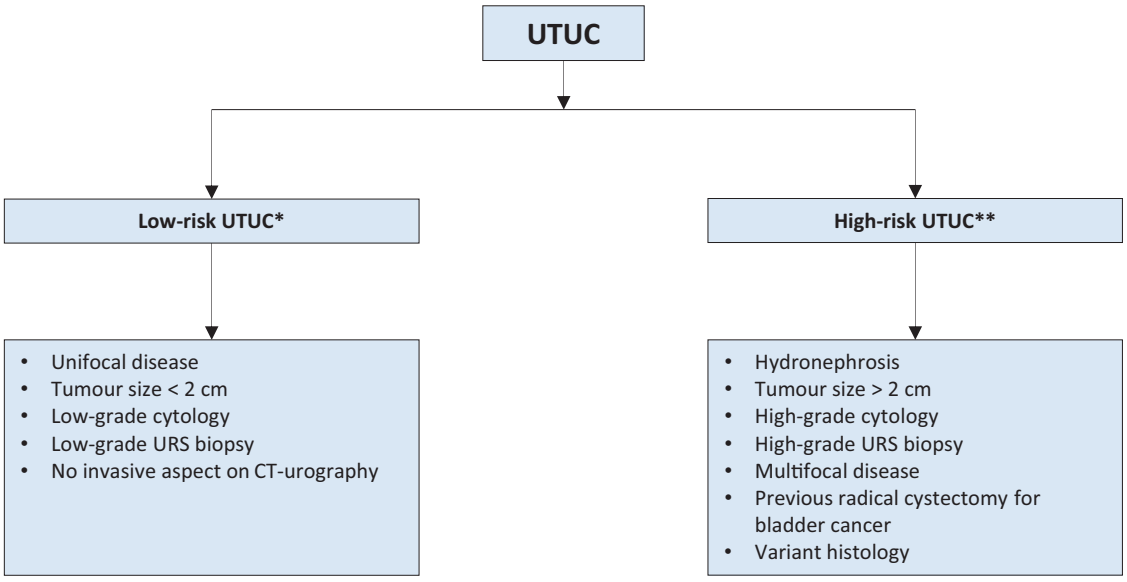
1. Patient-specific factors such as male gender, previous bladder cancer, smoking and pre-operative chronic kidney disease.
2. Tumour-specific factors such as positive pre-operative urinary cytology, ureteral location, multifocality, invasive pT stage, and necrosis.
3. Treatment-specific factors such as laparoscopic approach, extravesical bladder cuff removal, and positive surgical margins [120].

In addition, the use of diagnostic ureteroscopy has been associated with a higher risk of developing bladder recurrence after RNU [63], especially when primary UTUC was located in the renal pelvis [64] (LE: 3).

6.6 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 who are more suitable for kidney-sparing treatment rather than radical extirpative surgery [121, 122] (Figure 3).

Figure 6.2: Risk stratification of upper urinary tract urothelial carcinoma



CTU = computed tomography urography; URS = ureteroscopy; UTUC = upper urinary tract urothelial carcinoma.

*All these factors need to be present.

**Any of these factors need to be present

6.7 Summary of evidence and guidelines for prognosis

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

Recommendations	Strength rating
Use microsatellite instability as an independent molecular prognostic marker to help detect germline mutations and hereditary cancers.	Weak

7. DISEASE MANAGEMENT

7.1 Localised disease

*7.1.1 **Kidney-sparing surgery***

Kidney-sparing surgery (KSS) for low-risk UTUC reduces the morbidity associated with radical surgery, without compromising oncological outcomes and kidney function, as stated in a recent meta-analysis from the EAU Non-muscle-invasive Bladder Cancer Guidelines Panel [123] (Section 7.1.1.1). In low-risk cancers, it is the preferred approach with survival being similar after KSS vs. RNU [123]. This option should therefore be discussed in all low-risk cases, irrespective of the status of the contralateral kidney. In addition, it can also be considered in select patients with serious renal insufficiency or solitary kidney (LE: 3). Recommendations for kidney-sparing management of UTUC are listed in Section 7.1.1.1.

7.1.1.1 Guidelines for kidney-sparing management of upper tract urothelial cell carcinoma

Recommendations	Strength rating
Offer kidney-sparing management as primary treatment option to patients with low-risk tumours.	Strong
Offer kidney-sparing management to patients with high-risk distal ureteral tumours.	Weak
Offer kidney-sparing management to patients with solitary kidney and/or impaired renal function, providing that it will not compromise survival. This decision will have to be made on a case-by-case basis with the patient.	Strong
Use a laser for endoscopic treatment of upper tract urothelial carcinoma.	Weak

*7.1.2 **Ureteroscopy***

Endoscopic ablation can be considered in patients with clinically low-risk cancer in the following situations [124, 125]:

1. Laser generator and pliers available for biopsies [125, 126] (LE: 3);
2. In case a flexible (rather than a rigid) ureteroscope is available;
3. The patient is informed of the need for early (second look) [127], closer, more stringent, surveillance;
4. Complete tumour resection or destruction can be achieved.

Nevertheless, a risk of understaging and undergrading remains with endoscopic management [128].

7.1.2.1 Percutaneous access

Percutaneous management can be considered for low-risk UTUC in the renal pelvis [125, 129] (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 endoscopic tools such as distal-tip deflection of recent ureteroscopes [125, 129]. A risk of tumour seeding remains with a percutaneous access.

7.1.2.2 Segmental ureteral resection

Segmental ureteral resection with wide margins provides adequate pathological specimens for staging and grading while preserving the ipsilateral kidney. Lymphadenectomy can also be performed during segmental ureteral resection [123].

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 KSS for renal function preservation is necessary [130-132] (LE: 3).

Segmental resection of the iliac and lumbar ureter is associated with higher failure rates than for the distal pelvic ureter [40, 130, 131] (LE: 3).

Partial pyelectomy or partial nephrectomy is extremely rarely indicated. Open resection of tumours of the renal pelvis or calices has almost disappeared.

*7.1.3 **Adjuvant topical agents***

The antegrade instillation of bacillus Calmette-Guérin (BCG) vaccine or mitomycin C in the UUT 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 [106, 133] (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 but is not advisable since it often does not reach the renal pelvis [134].

*7.1.4 **Radical nephroureterectomy***

7.1.4.1 Open radical nephroureterectomy

Open RNU with bladder cuff excision is the standard for high-risk UTUC, regardless of tumour location [17] (LE: 3; Section 7.1.4.3). RNU must comply with oncological principles, that is, preventing tumour seeding by avoidance of entry into the urinary tract during resection [17]. Section 7.1.4.3 lists the recommendations for RNU.

Resection of the distal ureter and its orifice is performed because there is a considerable risk of tumour recurrence in this area [120]. 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 [130, 135].

Several techniques have been considered to simplify distal ureter resection, including pluck technique, stripping, transurethral resection of the intramural ureter, and intussusception. Except for ureteral stripping, none of these techniques is inferior to bladder cuff excision [16, 136, 137] (LE: 3).

7.1.4.2 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 [138, 139].

Several precautions may lower the risk of tumour spillage:

1. Avoid entering the urinary tract.
2. Avoid direct contact between instruments and the tumour.
3. Laparoscopic RNU must take place in a closed system. Avoid morcellation of the tumour and use an endobag for tumour extraction.
4. The kidney and ureter must be removed *en bloc* with the bladder cuff.
5. Invasive or large (T3/T4 and/or N+/M+) tumours are contraindications for laparoscopic RNU as the outcome is poorer compared to an open approach as stated in a meta-analysis by the EAU Guidelines Panel [8].

Laparoscopic RNU is safe in experienced hands when adhering to strict oncological principles. There is a tendency towards equivalent oncological outcomes after laparoscopic or open RNU [139-143] (LE: 3). Only one prospective randomised study has shown that laparoscopic RNU is not inferior to open RNU for non-invasive UTUC [144] (LE: 2). Oncological outcomes after RNU have not changed significantly over the past 3 decades despite staging and surgical refinements [145] (LE: 3). A robot-assisted laparoscopic approach can be considered, but solid data are still lacking [146, 147].

7.1.4.3 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	Strength rating
Perform radical nephroureterectomy in patients with high-risk tumours.	Strong
Technical steps of radical nephroureterectomy:	
Remove the bladder cuff.	Strong
Perform a lymphadenectomy in patients with high-risk tumours.	Weak
Offer a post-operative bladder instillation of chemotherapy to lower the intravesical recurrence rate.	Strong

7.1.5 Lymph node dissection

The anatomic sites of lymph node drainage have not yet been clearly defined. The use of a LND template is likely to have a greater impact on patient survival than the number of removed lymph nodes [148].

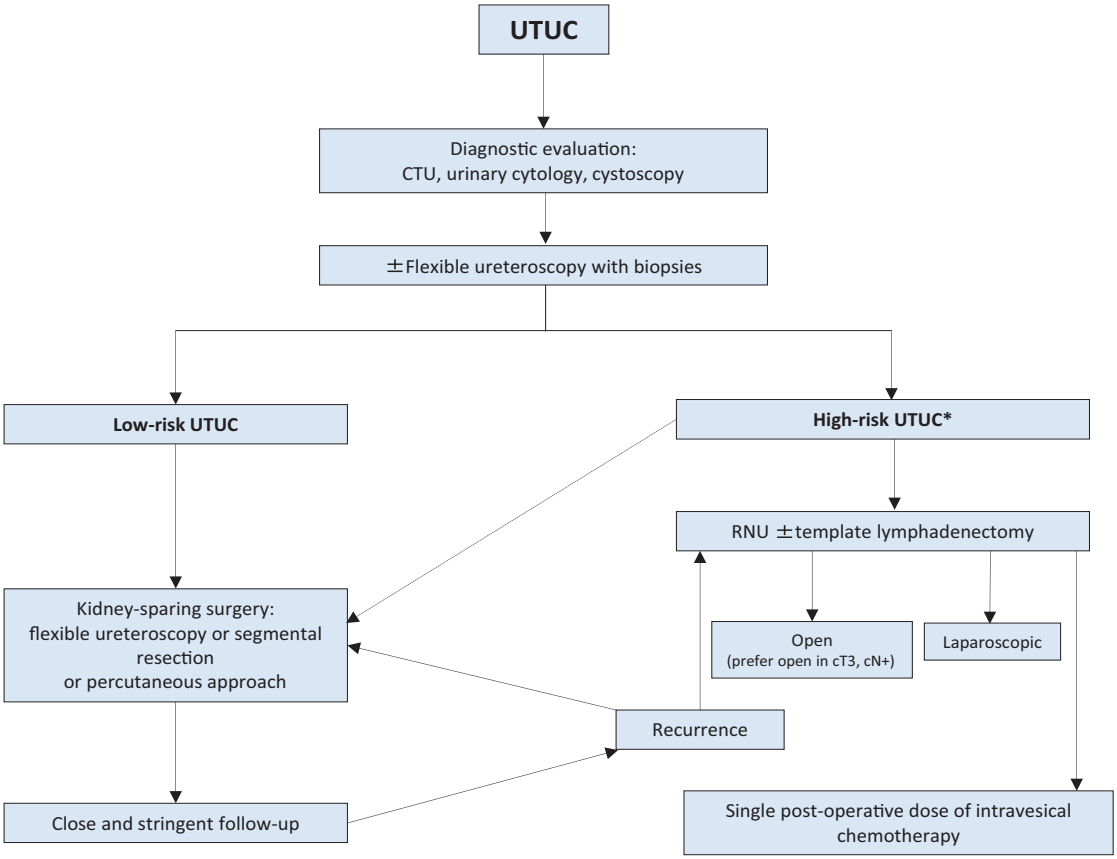
Lymph node dissection appears to be unnecessary in cases of TaT1 UTUC because LN retrieval is reported in only 2.2% of T1 vs. 16% of pT2–4 tumours [94, 149], so it is used infrequently [150]. An increase in the probability of lymph node–positive disease is related to pT classification [96]. However, it is likely that the true rate of node-positive disease has been under-reported because these data are retrospective. Lymph node dissection improves survival in patients with high-stage disease of the renal pelvis, if it is performed according to an anatomical template-based approach [9].

Despite available studies evaluating templates to date, it is not possible to standardise indication or extent of LND. LND 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) [94, 95].

7.1.6 Adjuvant bladder instillation

The rate of bladder recurrence after RNU for UTUC is 22–47%. Two prospective randomised trials and a meta-analysis [151] have demonstrated that a single post-operative dose of intravesical chemotherapy (mitomycin C, pirarubicin) soon after surgery (< 72 h) reduces the risk of bladder tumour recurrence within the first year post-RNU [152, 153] (LE: 2). Management is outlined in Figures 7.1 and 7.2.

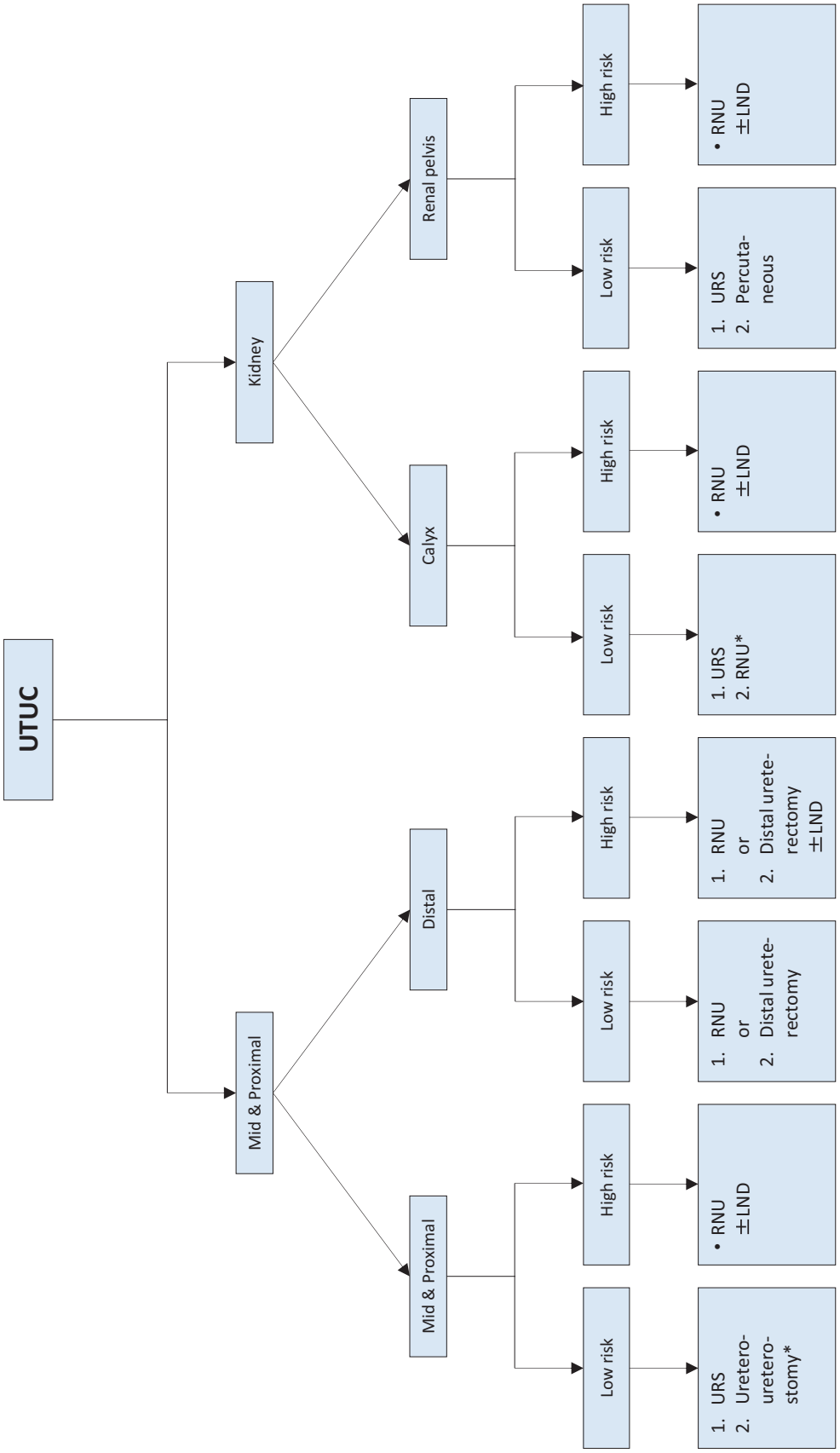
Figure 7.1: Proposed flowchart for the management of upper urinary tract urothelial cell carcinoma



CTU = computed tomography urography; RNU = radical nephroureterectomy; UTUC = upper urinary tract urothelial carcinoma.

*In patients with 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.
LND = lymph node dissection; RNU = radical nephroureterectomy; URS = ureteroscopy; UTUC = upper urinary tract urothelial carcinoma.
*In case not amendable to endoscopic management.

7.2 Advanced disease

*7.2.1 **Radical nephroureterectomy***

There is no oncological benefit for RNU alone in patients with metastatic UTUC except for palliative considerations [17] [96] (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 [154], but not all patients can receive adjuvant chemotherapy because of comorbidities and impaired renal function after radical surgery. Chemotherapy-related toxicity, particularly nephrotoxicity due to platinum derivatives, may significantly reduce survival in patients with post-operative renal dysfunction [155, 156].

There were no adverse effects of neoadjuvant chemotherapy for UTUC [157], although survival data need to mature and longer follow-up is awaited. In a select cohort of patients fit enough to receive systemic chemotherapy for metastatic UTUC, there was an overall survival (OS) benefit to combine chemotherapy and RNU vs. chemotherapy alone [158].

Second-line treatment in metastatic UTUC remains a challenge but in recent trials new immunotherapeutic drugs have demonstrated a response in a proportion of patients with UTUCs [159, 160].

After a recent comprehensive search of studies examining the role of perioperative chemotherapy for UTUC, there appears to be an OS and disease-free survival benefit for cisplatin-based adjuvant chemotherapy [161] (LE: 3). A recent study has assessed a clear OS benefit in patients who received adjuvant chemotherapy vs. observation after RNU for pT3/T4 and/or pN+ UTUC [162] (LE: 3).

*7.2.3 **Radiotherapy***

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

8. FOLLOW-UP

The risk of recurrence and death evolves during the follow-up period after surgery [164]. Stringent follow-up (Section 8.1) is mandatory to detect metachronous bladder tumours (probability increases over time [165], local recurrence, and distant metastases. Section 8.1 lists the summary of evidence and recommendations for follow-up of UTUC.

Surveillance regimens are based on cystoscopy and urinary cytology for > 5 years [13, 15, 16, 120]. Bladder recurrence is not a distant recurrence. When KSS is performed, the ipsilateral UUT requires careful follow-up due to the high risk of disease recurrence [126, 166, 167]. Despite endourological improvements, follow-up after kidney-sparing management is difficult, and frequent, repeated endoscopic procedures are necessary. As done in bladder cancer, a second look has been proposed after KSS but is not yet routine practice [127].

8.1 Summary of evidence and guidelines for the follow-up of UTUC

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	Strength rating
After radical nephroureterectomy:	
Low-risk tumours	
Perform cystoscopy at three months. If negative, perform subsequent cystoscopy nine months later and then yearly, for five years.	Weak

High-risk tumours	
Perform cystoscopy and urinary cytology at three months. If negative, repeat subsequent cystoscopy and cytology every three months for a period of two years, and every six months thereafter until five years, and then yearly.	Weak
Perform computed tomography urography every six months for two years, and then yearly.	Weak
After kidney-sparing management:	
Low-risk tumours	
Perform cystoscopy and computed tomography urography at three and six months, and then yearly for five years.	Weak
Perform ureteroscopy at three months.	Weak
High-risk tumours	
Perform cystoscopy, urinary cytology and computed tomography urography at three and six months, and then yearly.	Weak
Perform ureteroscopy and urinary cytology *in situ* at three and six months.	Weak

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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.

11. CITATION INFORMATION

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