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 upper urinary tract urothelial carcinoma (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 (UC). 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 2018 [4]. All documents are accessible through the EAU website Uroweb: http://uroweb.org/guideline/upperurinary-tract-urothelial-cell-carcinoma/.

1.4 Publication history & summary of changes

The first EAU Guidelines on UTUC were published in 2011. This 2020 publication presents a substantial update of the 2019 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 2020 print:

- Section 3.1 – Epidemiology – has been expanded, resulting changes in Figure 3.1 and the addition of two new recommendations

3.4 Summary of evidence and recommendations for epidemiology, aetiology and pathology

Summary of evidence	LE
Aristolochic acid and smoking exposure increases the risk for UTUC.	2
Patients with Lynch syndrome are at risk for UTUC.	3

Recommendations	Strength rating
Evaluate patient and family history based on the Amsterdam criteria to identify patients with upper tract urothelial carcinoma.	Weak
Evaluate patient exposure to smoking and aristolochic acid.	Weak

- Chapter 6 – Prognosis – additional information has been added, resulting in changes to Figure 6.1 and an additional recommendation.

6.7 Summary of evidence and guidelines for prognosis

Summary of evidence	LE
Chronological age should not preclude radical nephroureterectomy with curative intent, where indicated.	3
Important prognostic factors include hydronephrosis, tumour multifocality, size, stage, grade, lymph node metastasis, lymphovascular invasion and variant histology.	3

Recommendations	Strength rating
Use pre-operative factors to risk-stratify patients for therapeutic guidance.	Weak

- Chapter 7 – Disease management, has been restructured, including new information on adjuvant and neoadjuvant therapies. Both Figures 7.1 and 7.2 have been adapted and a number of new recommendations have been added.

7.1.6 Summary of evidence and guidelines for management of high-risk non-metastatic UTUC

Summary of evidence	LE
Failure to completely remove the bladder cuff increases the risk of bladder cancer recurrence.	3
Lymphadenectomy improves survival in muscle-invasive UTUC.	3
Peri-operative chemotherapy may improve survival.	3
Single post-operative intravesical instillation of chemotherapy lowers the bladder cancer recurrence rate.	1

Recommendations	Strength rating
Perform radical nephroureterectomy (RNU) in patients with high-risk non-metastatic upper tract urothelial carcinoma (UTUC).	Strong
Perform open RNU in non-organ-confined UTUC.	Weak
Remove the bladder cuff in its entirety.	Strong
Perform a template-based lymphadenectomy in patients with muscle-invasive UTUC.	Strong
Offer peri-operative chemotherapy to patients with muscle-invasive UTUC.	Weak
Deliver a post-operative bladder instillation of chemotherapy to lower the intravesical recurrence rate.	Strong

- Section 7.2 – Metastatic disease has been expanded to include the latest information on immunotherapy, both in a first- and second-line setting, resulting in a new summary table.

7.2.4 ***Summary of evidence and guidelines for the treatment of metastatic UTUC***

Summary of evidence	LE
Radical nephroureterectomy may improve quality of life and oncologic outcomes in select metastatic patients.	3
Cisplatin-based combination chemotherapy can improve median survival.	2
Single-agent and carboplatin-based combination chemotherapy are less effective than cisplatin-based combination chemotherapy in terms of complete response and survival.	3
Non-platinum combination chemotherapy has not been tested against standard chemotherapy in patients who are fit or unfit for cisplatin combination chemotherapy.	4
PD-1 inhibitor pembrolizumab has been approved for patients that have progressed during or after previous platinum-based chemotherapy based on the results of a phase III trial.	1b
PD-L1 inhibitor atezolizumab has been FDA approved for patients that have progressed during or after previous platinum-based chemotherapy based on the results of a phase II trial.	2a
PD-1 inhibitor nivolumab has been approved for patients that have progressed during or after previous platinum-based chemotherapy based on the results of a phase II trial.	2a
PD-1 inhibitor pembrolizumab has been approved for patients with advanced or metastatic UC ineligible for cisplatin-based first-line chemotherapy based on the results of a phase II trial but use of pembrolizumab is restricted to PD-L1 positive patients.	2a
PD-L1 inhibitor atezolizumab has been approved for patients with advanced or metastatic UC ineligible for cisplatin-based first-line chemotherapy based on the results of a phase II trial but use of atezolizumab is restricted to PD-L1 positive patients.	2a

Recommendations	Strength rating
Offer radical nephroureterectomy as a palliative treatment to symptomatic patients with resectable locally advanced tumours.	Weak
First-line treatment for cisplatin-eligible patients	
Use cisplatin-containing combination chemotherapy with GC, MVAC, preferably with G-CSF, HD-MVAC with G-CSF or PCG.	Strong
Do not offer carboplatin and non-platinum combination chemotherapy.	Strong
First-line treatment in patients unfit for cisplatin	
Offer checkpoint inhibitors pembrolizumab or atezolizumab depending on PDL-1 status.	Weak
Offer carboplatin combination chemotherapy if PD-L1 is negative.	Strong
Second-line treatment	
Offer checkpoint inhibitor (pembrolizumab) to patients with disease progression during or after platinum-based combination chemotherapy for metastatic disease.	Strong
Offer checkpoint inhibitor (atezolizumab) to patients with disease progression during or after platinum-based combination chemotherapy for metastatic disease.	Weak
Only offer vinflunine to patients for metastatic disease as second-line treatment if immunotherapy or combination chemotherapy is not feasible. Alternatively, offer vinflunine as third- or subsequent-treatment line.	Weak

GC = gemcitabine plus cisplatin; G-CSF = granulocyte colony-stimulating factor; HD-MVAC = high-dose methotrexate, vinblastine, adriamycin plus cisplatin; PD-L1 = programmed death ligand 1; PCG = paclitaxel, cisplatin, gemcitabine.

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 2020 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 June 20th (Cochrane)/June 26th 2018 (Embase) and May 31st 2019. 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 702 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 total of 56 new publications were added to the 2020 UTUC Guidelines print. A detailed search strategy is available online: http://uroweb.org/guideline/upper-urinarytract-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 LEs has been used [5].

For each recommendation within the guidelines there is an accompanying online strength rating form, based on a modified GRADE methodology [6, 7]. These forms address a number of key elements, namely:

1. The overall quality of the evidence which exists for the commendation references used in this text are graded according to the CEBM Levels of Evidence (see above) [5];
2. the magnitude of the effect (individual or combined effects);
3. the certainty of the results (precision, consistency, heterogeneity and other statistical or study related factors);
4. the balance between desirable and undesirable outcomes;
5. the impact of patient values and preferences on the intervention;
6. 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'. 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 [8].

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

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

2.2 Review

The UTUC Guidelines have been peer-reviewed prior to publication in 2016. The summary paper published in 2018 was peer-reviewed prior to publication [4].

3. EPIDEMIOLOGY, AETIOLOGY AND PATHOLOGY

3.1 Epidemiology

Urothelial carcinomas (UCs) are the fourth most common tumours in developed countries [9]. They can be located in the lower (bladder and urethra) and/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]. Upper urinary tract UCs are uncommon and account for only 5-10% of UCs [9] 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 [10]. Pyelocaliceal tumours are approximately twice as common as ureteral tumours whilst multifocal tumours are found in approximately 10-20% of cases [11]. The presence of concomitant carcinoma *in situ* of the upper tract is between 11 and 36% [10]. In 17% of cases, concurrent bladder cancer is present [12] whilst a prior history of bladder cancer is found in 41% of American men but in only 4% of Chinese men [13]. 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 [10]. Following treatment, recurrence in the bladder occurs in 22-47% of UTUC patients [14] compared with 2-6% in the contralateral upper tract [15].

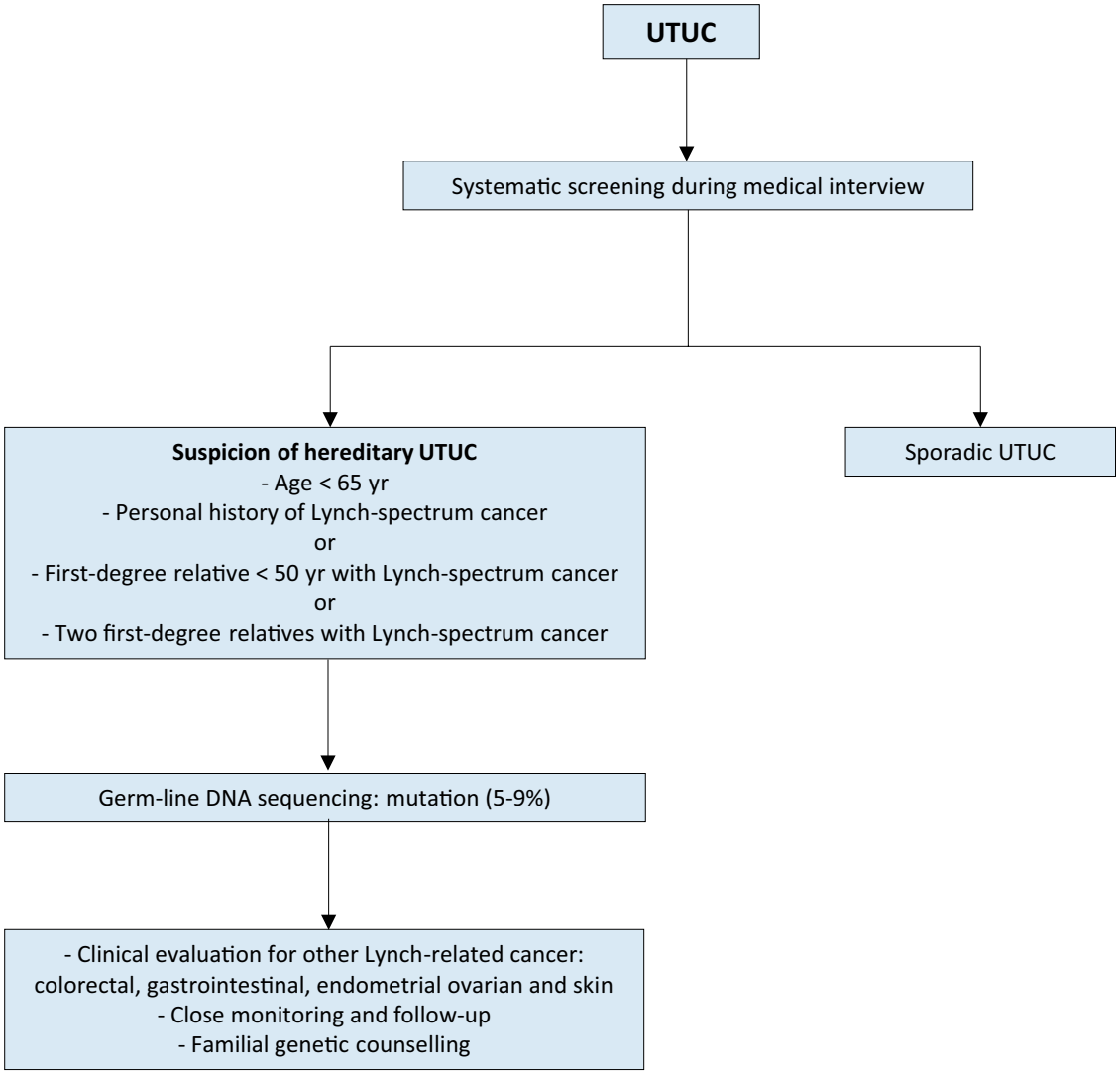
With regards to UTUC occurring following an initial diagnosis of bladder cancer, a series of 82 patients treated with bacillus Calmette-Guérin (BCG) who had regular upper tract imaging between years 1 and 3 showed a 13% incidence of UTUC, all of which were asymptomatic [16], whilst in another series of 307 patients without routine upper tract imaging the incidence was 25% [17]. More recently, a multicentre cohort study (n = 402) with a 50 month follow-up has demonstrated a UTUC incidence of 7.5% in NMIBC receiving BCG with predictors being intravesical recurrence and non-papillary tumour at transurethral resection of the bladder [16]. Following radical cystectomy for MIBC, 3-5% of patients develop a metachronous UTUC.

Approximately two-thirds of patients who present with UTUCs have invasive disease at diagnosis compared to 15-25% of patients presenting with bladder tumours [18]. Approximately 7% of patients present with metastasis [10, 19]. Upper urinary tract UCs have a peak incidence in individuals aged 70-90 years and are three times more common in men [20].

Upper tract UC and bladder cancer exhibit significant differences in the prevalence of common genomic alterations. In individual patients with a history of both tumours, bladder cancer and UTUC were always clonally related. Genomic characterisation of UTUC provides information regarding the risk of bladder recurrence and can identify tumours associated with Lynch syndrome [21].

The Amsterdam criteria are a set of diagnostic criteria used by doctors to help identify families which are likely to have Lynch syndrome [22]. In Lynch-related UTUC, immunohistochemistry analysis showed loss of protein expression corresponding to the disease-predisposing MMR (mismatch repair) gene mutation in 98% of the samples (46% were microsatellite instable and 54% microsatellite stable) [23]. The majority of tumours develop in MSH2 mutation carriers [24]. Patients identified at high risk for Lynch syndrome should undergo DNA sequencing for patient and family counselling [25, 26]. Germline mutations in DNA MMR genes defining Lynch syndrome, are found in 9% of patients with UTUC compared to 1% of patients with bladder cancer, linking UTUC to Lynch syndrome [27]. A recent study of 115 consecutive UTUC patients, reported that 13.9% screened positive for potential Lynch syndrome and 5.2% had confirmed Lynch syndrome [28]. This is one of the highest rates of undiagnosed genetic disease in urological cancers, which justifies screening of all patients under 65 presenting with UTUC and those with a family history of UTUC (see Figure 3.1) [29, 30].

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



UTUC = upper urinary tract urothelial carcinoma.

3.2 Risk factors

A number of environmental factors have been implicated in the development of UTUC [11, 31]. Published evidence in support of a causative role for these factors is not strong, with the exception of smoking and aristolochic acid. Tobacco exposure increases the relative risk of developing UTUC from 2.5 to 7.0 [32-34]. A large population-based study assessing familial clustering in relatives of UC patients, including 229,251 relatives of case subjects and 1197,552 relatives of matched control subjects, has demonstrated genetic or environmental roots independent of smoking-related behaviours. With more than a 9% of the cohort being UTUC patients, clustering was not seen in upper tract disease. This may suggest that the familial clustering of urothelial cancer is specific to lower tract cancers [35].

In Taiwan, the presence of arsenic in drinking water has been tentatively linked to UTUC [36]. Aristolochic acid, a nitrophenanthrene carboxylic acid produced by Aristolochia plants, exerts multiple effects on the urinary system. Aristolochic acid irreversibly injures renal proximal tubules resulting in chronic tubulointerstitial disease, while the mutagenic properties of this chemical carcinogen lead predominantly to UTUC [37-39]. Aristolochic acid has been linked recently to bladder cancer, renal cell carcinoma, hepatocellular carcinoma and intrahepatic cholangiocarcinoma [40]. Two routes of exposure to aristolochic acid are known: (i) environmental contamination of agricultural products by Aristolochia plants, as reported for Balkan endemic nephropathy [41]; and (ii) ingestion of Aristolochia-based herbal remedies [42, 43]. Aristolochia herbs are used worldwide, especially in China and Taiwan [39]. Following bioactivation, aristolochic acid reacts with genomic DNA to form aristolactam-deoxyadenosine adducts [44]; these lesions persist for decades in target tissues, serving as robust biomarkers of exposure [9]. These adducts generate a unique mutational spectrum, characterised by A>T transversions located predominately on the non-transcribed strand of DNA [40, 45].

However, fewer than 10% of individuals exposed to aristolochic acid develop UTUC [38].

Two recent retrospective series found that aristolochic acid-associated UTUC is more common in females [46, 47]. However, females with aristolochic acid UTUC have a better prognosis than their male counterparts.

Alcohol consumption is associated with development of UTUC. A large case-control study (1,569 cases and 506,797 controls) has evidenced a significantly higher risk of UTUC in ever-drinkers compared to never-drinkers (OR: 1.23; 95% CI: 1.08-1.40, p = 0.001). Compared to never-drinkers, the risk threshold for UTUC was > 15 gr. of alcohol/day. A dose-response was observed [48].

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. Upper urinary tract UCs may share some risk factors and described molecular pathways with bladder UC [21]. So far, two UTUC-specific polymorphisms have been reported [49].

3.3 Histology and classification

*3.3.1 **Histological types***

Upper urinary tract UC with pure non-urothelial histology is rare [50, 51] but variants are present in approximately 25% of cases [52, 53]. Pure squamous cell carcinoma of the urinary tract is often assumed to be associated with chronic inflammatory diseases and infections arising from urolithiasis [54-57]. Urothelial carcinoma with divergent squamous differentiation is present in approximately 15% of cases [55]. Upper urinary tract UCs with variant histology are often high-grade and have a worse prognosis compared with pure UC [53, 58]. Other variants, although rare, include sarcomatoid and UCs with inverted growth [59].

However, collecting duct carcinomas, which may seem to share similar characteristics with UCs, display a unique transcriptomic signature similar to renal cancer, with a putative cell of origin in the distal convoluted tubules. Therefore, collecting duct carcinomas are considered as renal tumours [60].

3.4 Summary of evidence and recommendations for epidemiology, aetiology and pathology

Summary of evidence	LE
Aristolochic acid and smoking exposure increases the risk for UTUC.	2
Patients with Lynch syndrome are at risk for UTUC.	3

Recommendations	Strength rating
Evaluate patient and family history based on the Amsterdam criteria to identify patients with upper tract urothelial carcinoma.	Weak
Evaluate patient exposure to smoking and aristolochic acid.	Weak

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) [61], 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 1 [62]. The regional lymph nodes (LNs) are the hilar and retroperitoneal nodes and, for the mid- and distal ureter, the pelvic nodes. Laterality does not affect N classification.

4.3 Tumour grade

In 2004, the WHO and the International Society of Urological Pathology published a new histological classification of UCs which provides a different patient stratification between individual categories compared

to the older 1973 WHO classification [63, 64]. In 2016, an update of the 2004 WHO grading classification was published without major changes [63]. These guidelines are still based on both the 1973 and 2004/2016 WHO classifications since most published data use the 1973 classification [61].

4.4 Future developments

A number of recent studies focussing on molecular classification have been able to demonstrate genetically different groups of UTUC by evaluating DNA, RNA and protein expression. Four molecular subtypes with distinct clinical behaviours were identified, but, as yet, it is unclear whether these subtypes will respond differently to treatment [65].

Table 1: TNM classification 2017 for upper tract urothelial cell carcinoma [62]

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).

5. DIAGNOSIS

5.1 Symptoms

The diagnosis of UTUC may be incidental or symptom related. The most common symptom is visible or nonvisible haematuria (70-80%) [66, 67]. Flank pain occurs in approximately 20% of cases [68, 69]. Systemic symptoms (including anorexia, weight loss, malaise, fatigue, fever, night sweats, or cough) associated with UTUC should prompt evaluation for metastases associated with a worse prognosis [68, 69].

5.2 Imaging

*5.2.1 **Computed tomography urography***

Computed tomography (CT) urography has the highest diagnostic accuracy of the available imaging techniques [70]. A meta-analysis of 13 studies comprising 1,233 patients revealed a pooled sensitivity of CT urography for UTUC of 92% (CI: 88-98) and a pooled specificity of 95% [71].

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 presence of enlarged LNs is highly predictive of metastases in UTUC [72].

*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 [73]. The sensitivity of MR urography is 75% after contrast injection for tumours < 2 cm [73]. 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. Computed tomography urography is generally preferred to MR urography for the diagnosis and staging of UTUC.

5.3 Cystoscopy and urinary cytology

Urethrocystocopy is an integral part of UTUC diagnosis to rule out concomitant bladder cancer [10, 12]. Abnormal cytology may indicate high-grade UTUC when bladder cystoscopy is normal, and in the absence of CIS in the bladder and prostatic urethra [1, 74, 75]. Cytology is less sensitive for UTUC than bladder tumours and should be performed selectively for the affected upper tract [76]. Retrograde ureteropyelography remains an option to detect UTUCs [70, 77, 78]. 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 [78, 79]. In a recent study, barbotage cytology detected up to 91% of cancers, being as effective as biopsy histology [80].

The sensitivity of fluorescence *in situ* hybridisation (FISH) for molecular abnormalities characteristic of UTUCs is approximately 50% and therefore its use in clinical practice remains unproven [81-83].

5.4 Diagnostic ureteroscopy

Flexible ureteroscopy (URS) is used to visualise the ureter, renal pelvis and collecting system and for biopsy of suspicious lesions. Presence, appearance and size of tumour can be determined using URS. In addition, ureteroscopic biopsies can determine tumour grade in 90% of cases with a low false-negative rate, regardless of sample size [84]. Undergrading may occur following diagnostic biopsy, making intensive follow-up necessary if kidney-sparing treatment is chosen [85]. Ureteroscopy also facilitates selective ureteral sampling for cytology *in situ* [78, 86, 87]. Stage assessment using ureteroscopic biopsy is inaccurate.

Combining ureteroscopic biopsy grade, imaging findings such as hydronephrosis, and urinary cytology may help in the decision-making process between radical nephroureterectomy (RNU) and kidney-sparing therapy [87, 88]. While some studies suggest a higher rate of intravesical recurrence after RNU in patients who underwent diagnostic URS pre-operatively [89, 90], one study did not [91].

Technical developments in flexible ureteroscopes and the use of novel imaging techniques improve visualisation and diagnosis of flat lesions [92]. Narrow-band imaging is a promising technique, but results are preliminary [88, 93, 94]. 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 [95, 96]. Recommendations for the diagnosis of UTUC are listed in Section 5.6.

5.5 Distant metastases

Prior to any treatment with curative intent, it is essential to rule out distant metastases. Computed tomography is the diagnostic technique of choice for lung- and abdominal staging for metastases [71].

5.6 Summary of evidence and guidelines for the diagnosis of UTUC

Summary of evidence	LE
The diagnosis and staging of UTUC is best done with computed tomography urography and URS.	2
Selective urinary cytology has high sensitivity in high-grade tumours, including carcinoma *in situ*.	3
Urethrocystoscopy can detect concomitant bladder cancer.	2

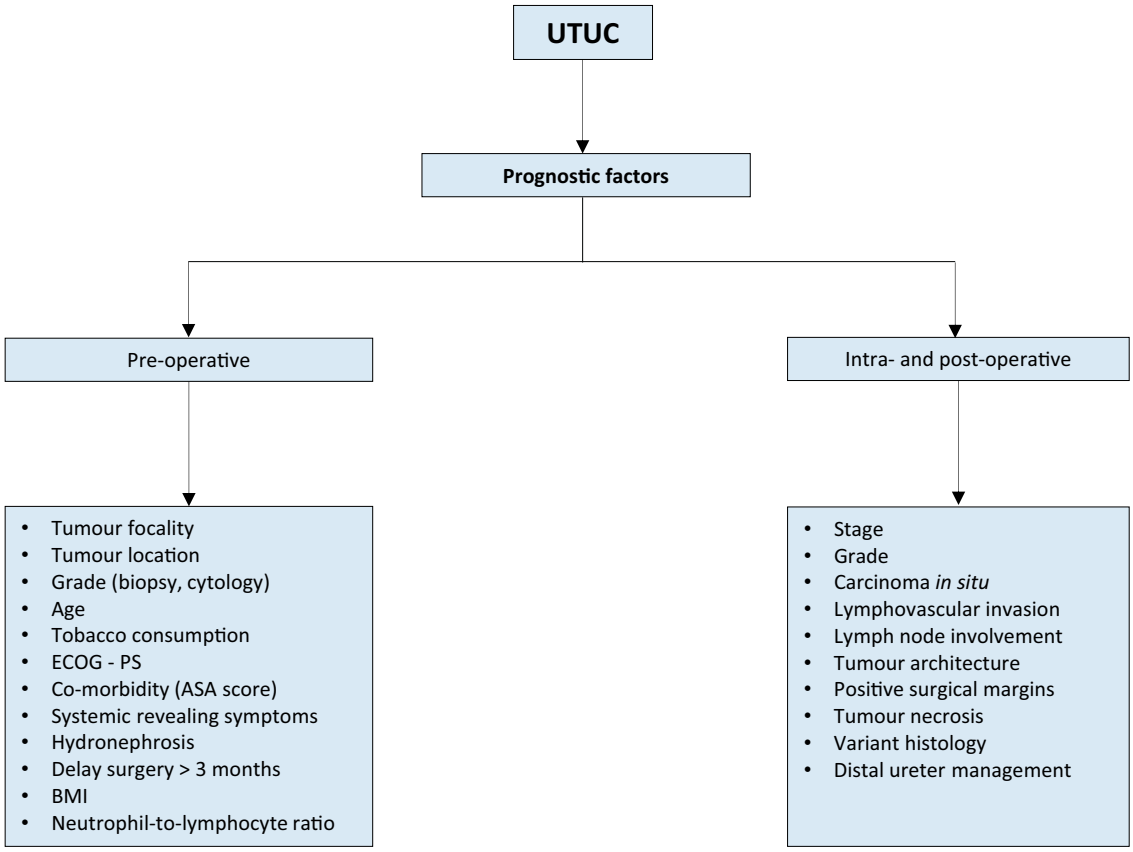
Recommendations	Strength rating
Perform a urethrocystoscopy to rule out bladder tumour.	Strong
Perform a computed tomography (CT) urography for diagnosis and staging.	Strong
Use diagnostic ureteroscopy and biopsy if imaging and cytology are not sufficient for the diagnosis and/or risk-stratification of the tumour.	Strong
Magnetic resonance urography may be used when CT is contra-indicated.	Weak

6. PROGNOSIS

6.1 Prognostic factors

Upper urinary tract UCs 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 UTUC [97-100]. The main prognostic factors are briefly listed in the text. Figure 6.1 shows a more exhaustive list of those patients with the most increased risk.

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; UTUC = upper urinary tract urothelial cell carcinoma.

6.2 Pre-operative factors

6.2.1 Age and gender

Older age at the time of RNU is independently associated with decreased cancer-specific survival (CSS) [98, 101, 102] (LE: 3). However, even elderly patients can be cured with RNU [103]. Therefore, chronological age alone should not be a contraindication to RNU [102, 103]. Gender has no impact on prognosis of UTUC [20, 98, 104].

6.2.2 Ethnicity

One multicentre study of academic centres did not show any difference in outcomes between races [105], but U.S. population-based studies have indicated that African-American patients have worse outcomes than other ethnicities (LE: 3). Whether this is related to access to care or biological and/or patterns of care remains unknown. Another study has demonstrated differences between Chinese and American patients at presentation (risk factor, disease characteristics and predictors of adverse oncologic outcomes) [13].

6.2.3 Tobacco consumption

Being a smoker at diagnosis increases the risk for disease recurrence and mortality after RNU [106, 107] and recurrence within the bladder [108] (LE: 3). There is a close relationship between tobacco consumption and prognosis; smoking cessation improves cancer control.

*6.2.4 **Tumour location, multifocality, size and hydronephrosis***

Initial location of the UTUC is a prognostic factor in some studies [109, 110] (LE: 3). After adjustment for the effect of tumour stage, patients with ureteral and/or multifocal tumours seem to have a worse prognosis than patients diagnosed with renal pelvic tumours [98, 109-114]. Hydronephrosis is associated with advanced disease and poor oncological outcome [68, 72, 79].

*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 [115-119] (LE: 3).

*6.2.6 **Other***

A higher American Society of Anesthesiologists score confers worse CSS after RNU [120] (LE: 3), as does poor performance status [121]. Obesity and higher body mass index adversely affect cancer-specific outcomes in patients treated with RNU [122] (LE: 3). High pre-treatment-derived neutrophil-lymphocyte ratio [123, 124] and low albumin [125] have been associated with worse cancer-specific mortality.

6.3 Post-operative factors

*6.3.1 **Tumour stage and grade***

The primary recognised prognostic factors are tumour stage and grade [18, 87, 98, 126, 127].

*6.3.2 **Lymph node involvement***

Lymph node metastasis and extranodal extension are powerful predictors of survival outcomes in UTUC [128, 129]. Lymph node dissection (LND) performed at the time of RNU allows for optimal tumour staging, although its curative role remains controversial [100, 129-131] (LE: 3).

*6.3.3 **Lymphovascular invasion***

Lymphovascular invasion (LVI) is present in approximately 20% of UTUCs and is an independent predictor of survival [132-134]. Lymphovascular invasion status should be specifically reported in the pathological reports of all UTUC specimens [132, 135, 136] (LE: 3).

*6.3.4 **Surgical margins***

Positive soft tissue surgical margin is associated with a higher disease recurrence after RNU. Pathologists should look for and report positive margins at the level of ureteral transection, bladder cuff, and around the tumour [137] (LE: 3).

*6.3.5 **Other pathological factors***

Extensive tumour necrosis (> 10% of the tumour area) is an independent prognostic predictor in patients who undergo RNU [138, 139] (LE: 3). The architecture of UTUC is also a strong prognosticator with sessile growth pattern being associated with worse outcome [140, 141] (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 [142, 143] (LE: 3). Macroscopic infiltration or invasion of peri-pelvic adipose tissue confers a higher risk of disease recurrence after RNU compared to microscopic infiltration of renal parenchyma [52, 144].

6.4 Molecular markers

Several studies have investigated the prognostic impact of molecular markers related to cell adhesion (E-cadherin [145] and CD24), microsatellite instability [146], cell differentiation [147, 148], angiogenesis, cell proliferation (Ki-67), epithelial-mesenchymal transition, mitosis), apoptosis, vascular invasion, programmed death(ligand) 1 (PD-1/PDL-1) expression [149] and c-MET protein [98, 150].

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

There are three pre-RNU models aiming at predicting which patient has muscle-invasive/non-organ-confined disease [151-153].

Five prognostic nomograms based on pathological characteristics are available [100, 154-158].

6.5.1 Bladder recurrence

A meta-analysis of available data has identified significant predictors of bladder recurrence after RNU [159] (LE: 3). Three categories of predictors of increased risk for bladder recurrence were identified:

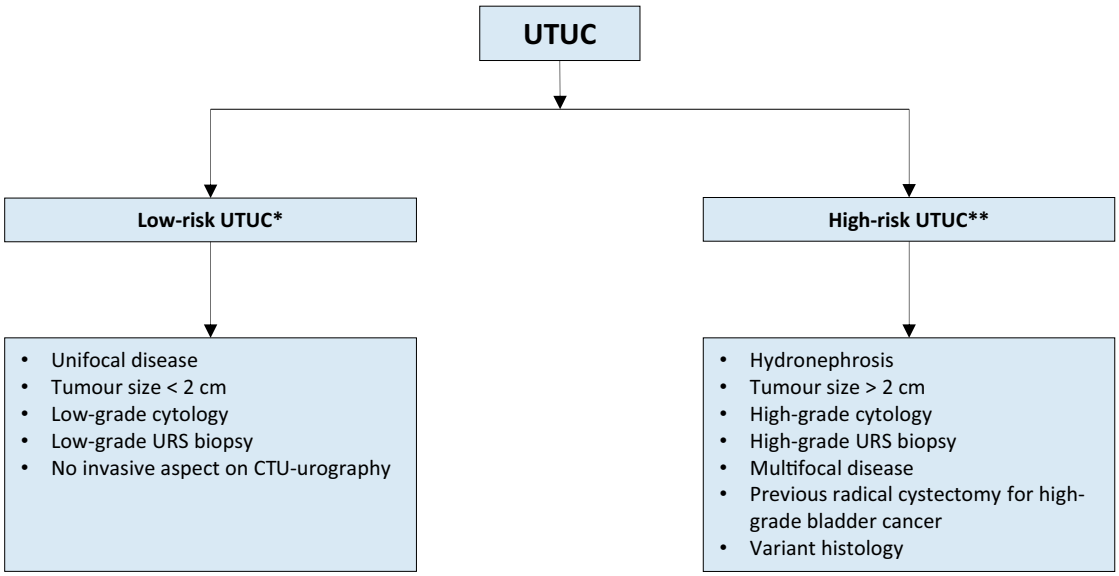
1. Patient-specific factors such as male gender, previous bladder cancer, smoking and pre-operative chronic kidney disease.
2. Tumour-specific factors such as positive pre-operative urinary cytology, ureteral location, multifocality, invasive pT stage, and necrosis.
3. Treatment-specific factors such as laparoscopic approach, extravesical bladder cuff removal, and positive surgical margins [159].

In addition, the use of diagnostic URS has been associated with a higher risk of developing bladder recurrence after RNU [89, 90] (LE: 3). Based on low-level evidence only, a single dose of intravesical chemotherapy after diagnostic/therapeutic ureteroscopy of non-metastatic UTUC has been suggested to lower the rate of intravesical recurrence, similarly to that after RNU [119-121].

6.6 Risk stratification of non-metastatic UTUC

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 patients who are more likely to benefit from kidney-sparing treatment [160, 161] (Figure 6.2).

Figure 6.2: Risk stratification of non-metastatic UTUC



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 the prognosis of UTUC

Summary of evidence	LE
Chronological age should not preclude radical nephroureterectomy with curative intent, where indicated.	3
Important prognostic factors include hydronephrosis, tumour multifocality, size, stage, grade, lymph node metastasis, lymphovascular invasion and variant histology.	3

Recommendations	Strength rating
Use pre-operative factors to risk-stratify patients for therapeutic guidance.	Weak

7. DISEASE MANAGEMENT

7.1 Localised non-metastatic disease

*7.1.1 **Kidney-sparing surgery***

Kidney-sparing surgery for low-risk UTUC reduces the morbidity associated with radical surgery (e.g. loss of kidney function), without compromising oncological outcomes [162]. In low-risk cancers, it is the preferred approach as survival is similar to that after RNU [162]. 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 a serious renal insufficiency or having a solitary kidney (LE: 3). Recommendations for kidney-sparing management of UTUC are listed in Section 7.1.1.5.

7.1.1.1 Ureteroscopy

Endoscopic ablation should be considered in patients with clinically low-risk cancer [163, 164]. A flexible ureteroscope is necessary in management of pelvicalyceal tumours [165]. The patient should be informed of the need and be willing to comply with an early second-look URS [166] and stringent surveillance; complete tumour resection or destruction is necessary [166]. Nevertheless, a risk of disease progression remains with endoscopic management due to the suboptimal performance of imaging and biopsy for risk stratification and tumour biology [167].

7.1.1.2 Percutaneous access

Percutaneous management can be considered for low-risk UTUC in the renal pelvis [164, 168] (LE: 3). This may also be offered for low-risk tumours in the lower caliceal system that are inaccessible or difficult to manage by flexible URS. However, this approach is being used less due to the availability of improved endoscopic tools such as distal-tip deflection of recent ureteroscopes [164, 168]. Moreover, a risk of tumour seeding remains with a percutaneous access.

7.1.1.3 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 [162]. Segmental resection of the proximal two-thirds of ureter is associated with higher failure rates than for the distal ureter [169, 170] (LE: 3).

Distal ureterectomy with ureteroneocystostomy 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 desired [99, 169, 170] (LE: 3). A total ureterectomy with an ileal-ureteral substitution is technically feasible, but only in selected cases when a renal-sparing procedure is mandatory and the tumour is low risk [171].

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

7.1.1.4 Upper urinary tract instillation of topical agents

The antegrade instillation of BCG or mitomycin C in the upper urinary tract via percutaneous nephrostomy after complete tumour eradication has been studied for CIS after kidney-sparing management [143, 172] (LE: 3). Retrograde instillation through a single J open-ended ureteric stent is also used. Both the antegrade and retrograde approach 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 this approach is suboptimal because the drug often does not reach the renal pelvis [173-176]. A recently published systematic review and meta-analysis, assessing the oncologic outcomes of patients with papillary UTUC or CIS of the upper tract treated with kidney-sparing surgery and adjuvant endocavitary treatment, analysed the effect of adjuvant therapies (i.e., chemotherapeutic agents and/or immunotherapy with BCG) after kidney-sparing surgery for papillary non-invasive (Ta-T1) UTUCs and of adjuvant BCG for the treatment of UT CIS, finding no difference between the method of drug administration (antegrade vs. retrograde vs. combined approach) in terms of recurrence, progression, CSS, and overall survival (OS). Furthermore, the recurrence rates following adjuvant instillations are comparable to those reported in the literature in untreated patients, questioning their efficacy [177]. The analyses were based on retrospective small studies suffering from publication and reporting bias.

7.1.1.5 Guidelines for kidney-sparing management of UTUC

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 tumours limited to the distal ureter.	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

7.1.2 Management of high-risk non-metastatic UTUC

7.1.2.1 Surgical approach

7.1.2.1.1 Open radical nephroureterectomy

Open RNU with bladder cuff excision is the standard treatment of high-risk UTUC, regardless of tumour location [18] (LE: 3). Radical nephroureterectomy must be performed according to oncological principles preventing tumour seeding [18]. Section 7.1.6 lists the recommendations for RNU.

7.1.2.1.2 Minimal invasive 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 [178, 179]. 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. perform the procedure 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 minimal-invasive RNU as the outcome is worse compared to an open approach [180, 181].

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 [179, 182-185] (LE: 3). One prospective randomised study has shown that laparoscopic RNU is inferior to open RNU for non-organ confined UTUC [181] (LE: 2). Oncological outcomes after RNU have not changed significantly over the past three decades despite staging and surgical refinements [186] (LE: 3). A robot-assisted laparoscopic approach can be considered with recent data suggesting oncologic equivalence with the other approaches [187-189].

7.1.2.1.3 Management of bladder cuff

Resection of the distal ureter and its orifice is performed because there is a considerable risk of tumour recurrence in this area and in the bladder [159, 169, 190-192]. Several techniques have been considered to simplify distal ureter resection, including the pluck technique, stripping, transurethral resection of the intramural ureter, and intussusception. None of these techniques has convincingly been shown to be equal to complete bladder cuff excision [15, 190, 191] (LE: 3).

7.1.2.1.4 Lymph node dissection

The use of an LND template is likely to have a greater impact on patient survival than the number of removed LNs [193]. Template-based and completeness of LND improves CSS in patients muscle-invasive disease and reduces the risk of local recurrence [194]. Even in clinically [195] and pathologically [196] node-negative patients, LND improves survival.

The risk of LN metastasis increases with advancing tumour stage [130]. Lymph node dissection appears to be unnecessary in cases of TaT1 UTUC because of the low risk of LN metastasis [197-200], however, tumour staging is inaccurate pre-operatively; therefore a template-based LND should be offered to all patients who are planned for RNU. The templates for LND have been described [194, 201, 202].

7.1.3 ***Peri-operative chemotherapy***

7.1.3.1 Neoadjuvant chemotherapy

Several retrospective studies evaluating the role of neoadjuvant chemotherapy have shown promising pathological downstaging and complete response rates [203-207]. In addition, neoadjuvant chemotherapy has

been shown to result in lower disease recurrence and mortality rates compared to RNU alone [208-210]. No randomised controlled trials have yet been published.

7.1.3.2 Adjuvant chemotherapy

Conflicting results are available from retrospective studies evaluating adjuvant chemotherapy [211-213]. A population-based study has shown improved OS rates in pT3/T4 and/or pN+ patients (n = 3,253) [214], while a multicentre cohort study did not in pT2-T4 and/or pN+ patients (n = 1,544) [212].

The main limitation of using adjuvant chemotherapy for advanced UTUC remains the limited ability to deliver full dose cisplatin-based regimen after RNU, given that this surgical procedure is likely to impact renal function [215, 216]. Promising phase II prospective randomised data on the benefit of platinum-based adjuvant chemotherapy for pT2-4, N0-3M0 UTUC has been reported at meetings, with full publication pending.

*7.1.4 **Adjuvant Radiotherapy after radical nephroureterectomy***

Adjuvant radiation therapy has been suggested to control loco-regional disease after surgical removal. The data remains controversial and insufficient for conclusions [217-220]. Moreover, its additive value to chemotherapy remains questionable [219].

*7.1.5 **Post-operative bladder instillation***

The rate of bladder recurrence after RNU for UTUC is 22-47% [161, 191]. Two prospective randomised trials [221, 222] and a meta-analysis [223] have demonstrated that a single post-operative dose of intravesical chemotherapy (mitomycin C, pirarubicin) 2-10 days after surgery reduces the risk of bladder tumour recurrence within the first years post-RNU (LE: 2). Prior to instillation, a cystogram might be considered in case of any concerns about extravasation.

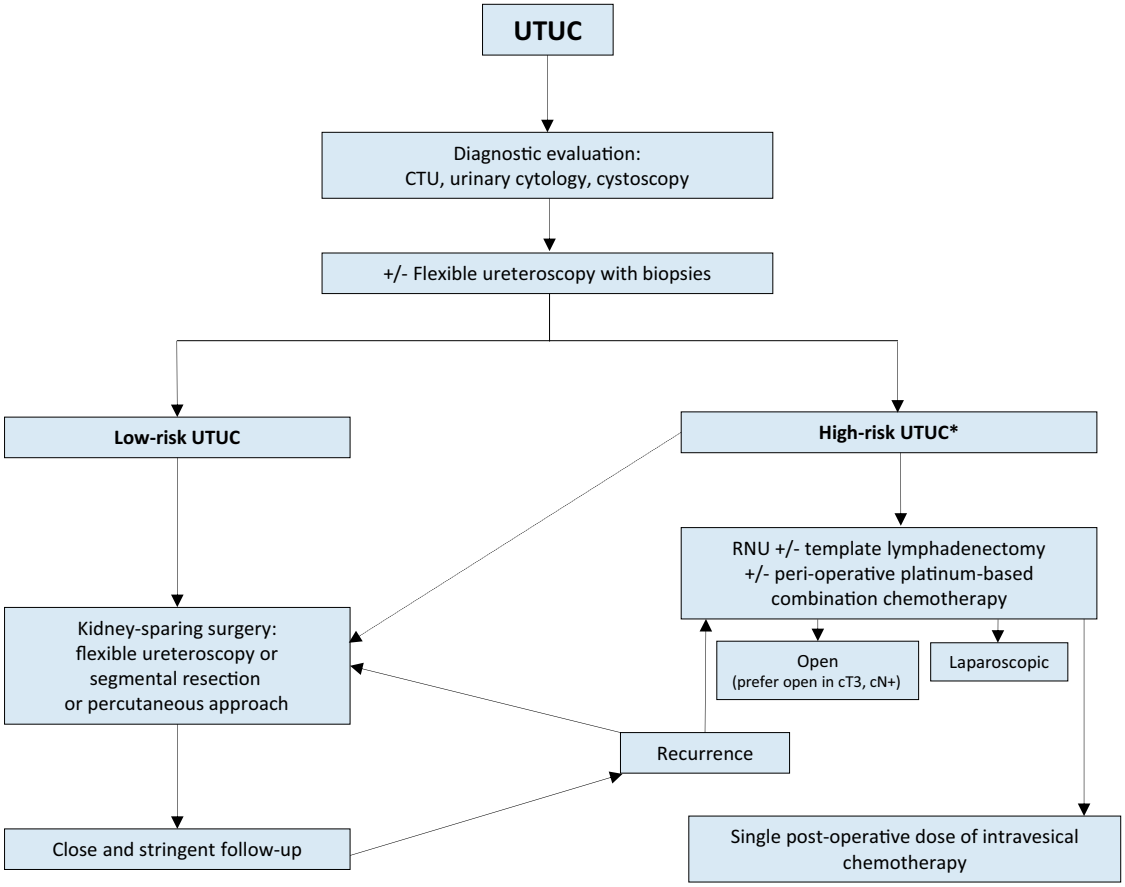
Whilst there is no direct evidence supporting the use of intravesical instillation of chemotherapy after kidney-sparing surgery, single-dose chemotherapy might be effective in that setting as well (LE: 4). Management is outlined in Figures 7.1 and 7.2.

*7.1.6 **Summary of evidence and guidelines for the management of high-risk non-metastatic UTUC***

Summary of evidence	**LE**
Radical nephroureterectomy is the standard treatment for high-risk UTUC, regardless of tumour location.	2
Open, laparoscopic and robotic approaches have similar oncological outcomes for organ-confined UTUC.	2
Failure to completely remove the bladder cuff increases the risk of bladder cancer recurrence.	3
Lymphadenectomy improves survival in muscle-invasive UTUC.	3
Peri-operative chemotherapy may improve survival.	3
Single post-operative intravesical instillation of chemotherapy lowers the bladder cancer recurrence rate.	1

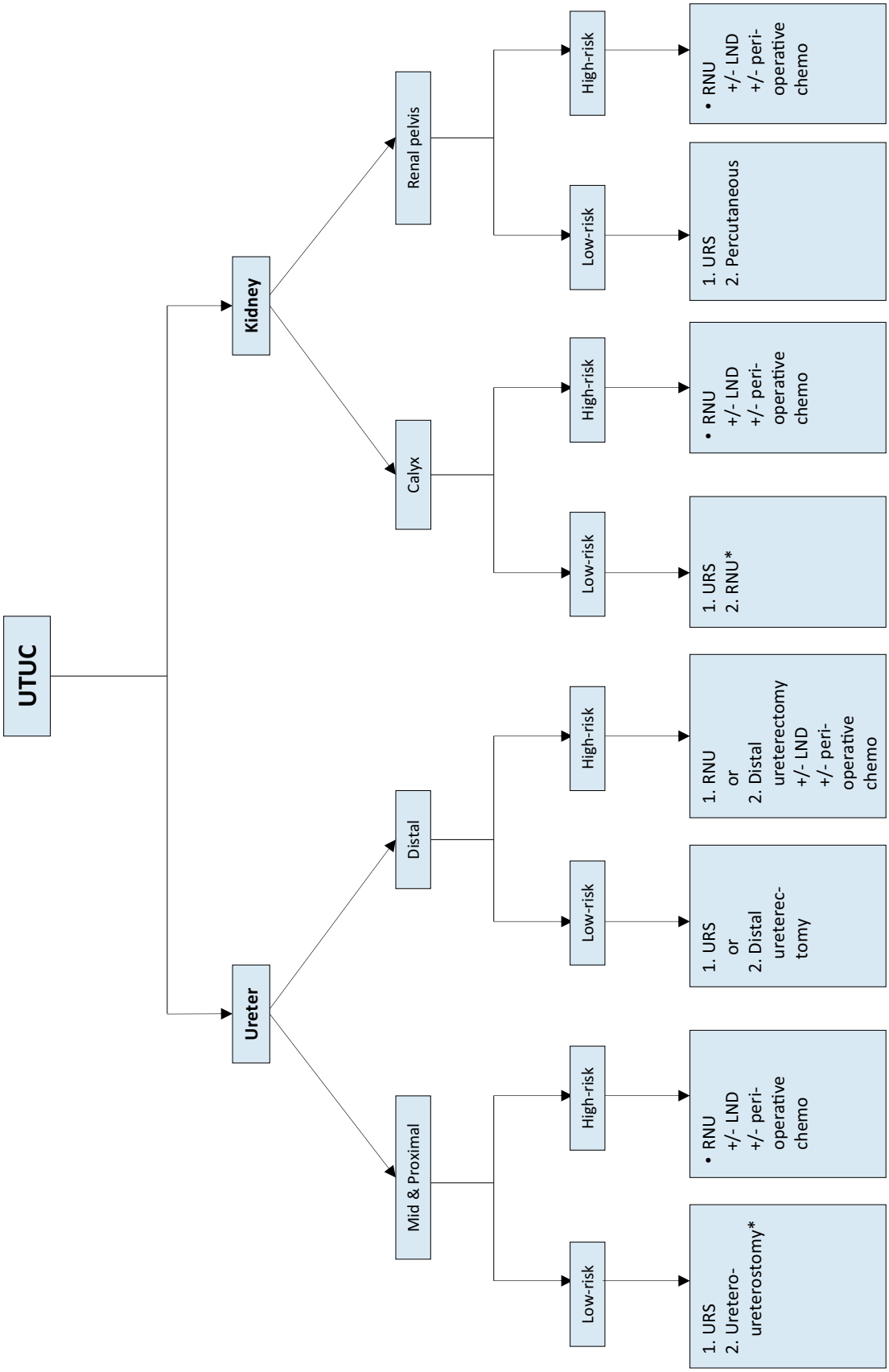
Recommendations	**Strength rating**
Perform radical nephroureterectomy (RNU) in patients with high-risk non-metastatic upper tract urothelial carcinoma (UTUC).	Strong
Perform open RNU in non-organ confined UTUC.	Weak
Remove the bladder cuff in its entirety.	Strong
Perform a template-based lymphadenectomy in patients with muscle-invasive UTUC.	Strong
Offer peri-operative chemotherapy to patients with muscle-invasive UTUC.	Weak
Deliver a post-operative bladder instillation of chemotherapy to lower the intravesical recurrence rate.	Strong

Figure 7.1: Proposed flowchart for the management of UTUC



**In patients with solitary kidney, consider a more conservative approach.*
CTU = computed tomography urography; RNU = radical nephroureterectomy;
UTUC = upper urinary tract urothelial carcinoma.

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.*
LND = lymph node dissection; RNU = radical nephroureterectomy; URS = ureteroscopy;
UTUC = upper urinary tract urothelial carcinoma.

7.2 Metastatic disease

*7.2.1 **Radical nephroureterectomy***

The role of RNU in the treatment of patients with metastatic UTUC has recently been explored in several observational studies [224-227]. Although evidence remains very limited, RNU may be associated with cancer-specific [224, 226, 227] and OS benefit in selected patients, especially those fit enough to receive cisplatin-based chemotherapy [225, 226]. It is noteworthy that these benefits may be limited to those with only one metastatic site [226]. Nonetheless, given the high risk of bias of the observational studies addressing RNU for metastatic UTUC, indications for RNU in this setting should mainly be reserved for palliative patients, aimed at controlling symptomatic disease [17, 106] (LE: 3). In patients who have a partial or complete response to induction chemotherapy, RNU may be discussed with the patient.

*7.2.2 **Metastasectomy***

There is no UTUC-specific study supporting the role of metastasectomy in patients with advanced disease. However, several reports including both UTUC and bladder cancer patients suggested that resection of metastatic lesions could be safe and oncologically beneficial in selected patients with a life expectancy of more than six months [228-230]. This was confirmed in the most recent and largest study to date [231]. Nonetheless, in the absence of data from randomised controlled trials, patients should be evaluated on an individual basis and the decision to perform a metastasectomy (surgically or otherwise) should be done in a shared decision-making process with the patient.

*7.2.3 **Systemic treatments***

7.2.3.1 First-line setting

Extrapolating from the bladder cancer literature and small, single-centre UTUC studies, platinum-based combination chemotherapy – especially using cisplatin – might be efficacious for first-line treatment of metastatic UTUC. A retrospective analysis of three RCTs showed that primary tumour location in the lower- or upper urinary tract had no impact on progression-free or OS in patients with locally advanced or metastatic UC treated with platinum-based combination chemotherapy [232].

In addition, the role of immunotherapy has been evaluated in the first-line setting for cisplatin-ineligible UTUC patients but limited data is available in the literature. First, a single-arm phase II trial including 370 patients showed that for the subset of those with UTUC (n = 69/19%), the objective response rate was 22% [233]. In the overall cohort, a PD-L1 expression of 10% was associated with a higher frequency of response to pembrolizumab, which had relative acceptable toxicity. Second, atezolizumab was associated with an objective response rate of 39% in 33 (27.7%) cisplatin-ineligible patients with metastatic UTUC included in a single-arm phase II trial (n = 119) [234]. Median OS in the overall cohort was 15.9 months and toxicity was relatively acceptable. No other data are currently available in the first-line setting but several phase III trials are currently testing pembrolizumab (NCT02853305 [235]) atezolizumab (NCT02807636 [236]) or durvalumab (NCT02516241 [237]) alone, and immunotherapy combinations with nivolumab (NCT03036098 [238]), durvalumab (NCT02516241 [237]) or pembrolizumab (NCT02178722 [239]) for patients with metastatic UC including those with UTUC.

7.2.3.2 Second-line setting

Similar to the bladder cancer setting, second-line treatment of metastatic UTUC remains challenging. In a *post-hoc* subgroup analysis of locally advanced or metastatic UC, vinflunine was reported to be as effective in UTUC as for bladder cancer progressing after cisplatin-based chemotherapy [240].

More importantly, a phase III RCT including 542 patients who received prior platinum-based chemotherapy for advanced UC showed that pembrolizumab could decrease the risk of death by almost 50% in those with UTUC (n = 75, 13.8%), although these results were borderline significant [241]. The objective response rate was 21.1% in the overall cohort and median OS was 10.3 months. Interestingly, although no subgroup analysis was available for UTUC patients (n = 65/21%) a single-arm phase II trial demonstrated that atezolizumab has durable activity associated with PD-L1 expression on immune cells in patients with metastatic UC [242]. The objective response rate was 26% in the group of those overexpressing PD-L1 and 15% in the overall population. However, a phase III RCT showed that it was not associated with prolonged OS as compared to chemotherapy in patients overexpressing PD-L1¬including 51 (21.8%) with UTUC, despite a more favourable safety profile [243].

Other immunotherapies such as nivolumab [244], avelumab [245, 246] and durvalumab [247] have shown objective response rates ranging from 17.8% [247] to 19.6% [244] and median OS ranging from 7.7 months to 18.2 months in patients with platinum-resistant metastatic UC overall. These results were obtained from single-arm phase I or II trials only and the number of UTUC patients included in these studies was only specified in evaluating avelumab (n = 7/15.9%) [246] without any subgroup analysis based on primary tumour location.

The immunotherapy combination of nivolumab plus ipilimumab has shown significant anti-tumour activity with objective response rate up to 38% in a phase I/II multicentre trial including 78 patients with metastatic UC progressing after platinum-based chemotherapy [248]. Although UTUC patients were included in this trial, no subgroup analysis was available. Other immunotherapy combinations may be effective in the second-line setting but data are currently limited [249].

7.2.4 Summary of evidence and guidelines for the treatment of metastatic UTUC

Summary of evidence	LE
Radical nephroureterectomy may improve quality of life and oncologic outcomes in select metastatic patients.	3
Cisplatin-based combination chemotherapy can improve median survival.	2
Single-agent and carboplatin-based combination chemotherapy are less effective than cisplatin-based combination chemotherapy in terms of complete response and survival.	3
Non-platinum combination chemotherapy has not been tested against standard chemotherapy in patients who are fit or unfit for cisplatin combination chemotherapy.	4
PD-1 inhibitor pembrolizumab has been approved for patients that have progressed during or after previous platinum-based chemotherapy based on the results of a phase III trial.	1b
PD-L1 inhibitor atezolizumab has been FDA approved for patients that have progressed during or after previous platinum-based chemotherapy based on the results of a phase II trial.	2a
PD-1 inhibitor nivolumab has been approved for patients that have progressed during or after previous platinum-based chemotherapy based on the results of a phase II trial.	2a
PD-1 inhibitor pembrolizumab has been approved for patients with advanced or metastatic UC ineligible for cisplatin-based first-line chemotherapy based on the results of a phase II trial but use of pembrolizumab is restricted to PD-L1 positive patients.	2a
PD-L1 inhibitor atezolizumab has been approved for patients with advanced or metastatic UC ineligible for cisplatin-based first-line chemotherapy based on the results of a phase II trial but use of atezolizumab is restricted to PD-L1 positive patients.	2a

Recommendations	Strength rating
Offer radical nephroureterectomy as a palliative treatment to symptomatic patients with resectable locally advanced tumours.	Weak
First-line treatment for cisplatin-eligible patients	
Use cisplatin-containing combination chemotherapy with GC, MVAC, preferably with G-CSF, HD-MVAC with G-CSF or PCG.	Strong
Do not offer carboplatin and non-platinum combination chemotherapy.	Strong
First-line treatment in patients unfit for cisplatin	
Offer checkpoint inhibitors pembrolizumab or atezolizumab depending on PD-L1 status.	Weak
Offer carboplatin combination chemotherapy if PD-L1 is negative.	Strong
Second-line treatment	
Offer checkpoint inhibitor (pembrolizumab) to patients with disease progression during or after platinum-based combination chemotherapy for metastatic disease.	Strong
Offer checkpoint inhibitor (atezolizumab) to patients with disease progression during or after platinum-based combination chemotherapy for metastatic disease.	Strong
Only offer vinflunine to patients for metastatic disease as second-line treatment if immunotherapy or combination chemotherapy is not feasible. Alternatively, offer vinflunine as third- or subsequent-treatment line.	Strong

GC = gemcitabine plus cisplatin; G-CSF = granulocyte colony-stimulating factor; HD-MVAC = high-dose methotrexate, vinblastine, adriamycin plus cisplatin; PD-L1 = programmed death ligand 1; PCG = paclitaxel, cisplatin, gemcitabine.

8. FOLLOW-UP

The risk of recurrence and death evolves during the follow-up period after surgery [250]. Stringent follow-up (Section 8.1) is mandatory to detect metachronous bladder tumours (probability increases over time [251]), local recurrence, and distant metastases. Section 8.1 presents the summary of evidence and recommendations for follow-up of UTUC.

Surveillance regimens are based on cystoscopy and urinary cytology for > 5 years [12, 14, 15, 161]. Bladder recurrence is not considered a distant recurrence. When kidney-sparing surgery is performed, the ipsilateral UUT requires careful follow-up due to the high risk of disease recurrence [165, 252, 253]. Despite endourological improvements, follow-up after kidney-sparing management is difficult and frequent, and repeated endoscopic procedures are necessary. As done in bladder cancer, a second look has been proposed after kidney-sparing surgery but is not yet routine practice [2, 166].

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

Summary of evidence	LE
Follow-up is more frequent and more stringent 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 (CT) urography and chest CT every six months for two years, and then yearly.	Weak
After kidney-sparing management	
Low-risk tumours	
Perform cystoscopy and CT urography at three and six months, and then yearly for five years.	Weak
Perform ureteroscopy (URS) at three months.	Weak
High-risk tumours	
Perform cystoscopy, urinary cytology, CT urography and chest CT at three and six months, and then yearly.	Weak
Perform URS 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/.

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11. CITATION INFORMATION

The format in which to cite the EAU Guidelines will vary depending on the style guide of the journal in which the citation appears. Accordingly, the number of authors or whether, for instance, to include the publisher, location, or an ISBN number may vary.

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