

# **EAU Guidelines on Upper Urinary Tract Urothelial Carcinoma**

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# 1. INTRODUCTION

## 1.1 Aim and scope

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). In the course of 2021 two patient representatives have formally joined the NMIBC Panel. All involved in the production of this document have submitted potential conflict of interest statements, which can be viewed on the EAU website Uroweb: <https://uroweb.org/guideline/upper-urinary-tract-urothelial-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 2020 [4]. All documents are accessible through the EAU website Uroweb: <https://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. This 2022 publication presents a limited update of the 2021 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 2022 print can be found in:

- Section 3.1 – Epidemiology, due to the inclusion of additional data on mismatch repair testing, Figure 3.1: Selection of patients with UTUC for Lynch syndrome screening during the first medical interview, was revised.
- Chapter 6 – Prognosis, considerable data has been added;
- 7.1.2 Management of high-risk non-metastatic UTUC – New Section 7.1.3.2.2 Immunotherapy, was added.
- 7.2.3 Systemic treatments. This section has been completely restructured and updated, resulting in a number of changes to the Summary of changes and guidelines for the treatment of metastatic UTUC.

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

Summary of evidence	LE
Cisplatin-containing combination chemotherapy is standard in advanced or metastatic patients fit enough to tolerate cisplatin.	1b
Maintenance avelumab is associated with an OS advantage compared with best supportive care in patients who did not have disease progression after 4 to 6 cycles of gemcitabine plus cisplatin or carboplatin.	1b
PD-1 inhibitor pembrolizumab has been approved for patients who have progressed during or after previous platinum-based chemotherapy and did not receive previous immune therapy based on the results of a phase III trial.	1b

PD-L1 inhibitor atezolizumab has been approved for patients that have progressed during or after previous platinum-based chemotherapy and did not receive previous immune therapy 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 and did not receive previous immune therapy based on the results of a phase II trial.	2a
Erdafitinib improves OS in platinum-refractory patients with locally advanced or metastatic UC and FGFR DNA genomic alterations ( <i>FGFR2</i> or 3 mutations, or <i>FGFR3</i> fusions).	2a

Recommendation	Strength rating
<b>First-line treatment for cisplatin-eligible patients</b>	
Use maintenance avelumab in patients who did not have disease progression after 4 to 6 cycles of gemcitabine plus cisplatin.	Strong
<b>First-line treatment in patients unfit for cisplatin</b>	
Use maintenance avelumab in patients who did not have disease progression after 4 to 6 cycles of gemcitabine plus carboplatin.	Strong
<b>Second-line treatment</b>	
Offer erdafitinib in platinum-refractory tumours with FGFR alterations.	Strong

FGFR = fibroblast growth factor receptors.

## 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 2022 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 May 29<sup>th</sup> 2020 and June 8<sup>th</sup> 2021. 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 823 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 45 new publications were included in the 2022 UTUC Guidelines print. A detailed search strategy is available online: <https://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 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 recommendation [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; <https://uroweb.org/guidelines/policies-and-methodological-documents/>.

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

## 2.2 Review

The 2021 UTUC Guidelines have been peer-reviewed prior to publication.

# 3. EPIDEMIOLOGY, AETIOLOGY AND PATHOLOGY

## 3.1 Epidemiology

Urothelial carcinomas are the sixth 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, 11]. Pyelocaliceal tumours are approximately twice as common as ureteral tumours and multifocal tumours are found in approximately 10–20% of cases [12]. 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 [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 [10]. Following treatment, recurrence in the bladder occurs in 22–47% of UTUC patients, depending on initial tumour grade [15] compared with 2–5% in the contralateral upper tract [16].

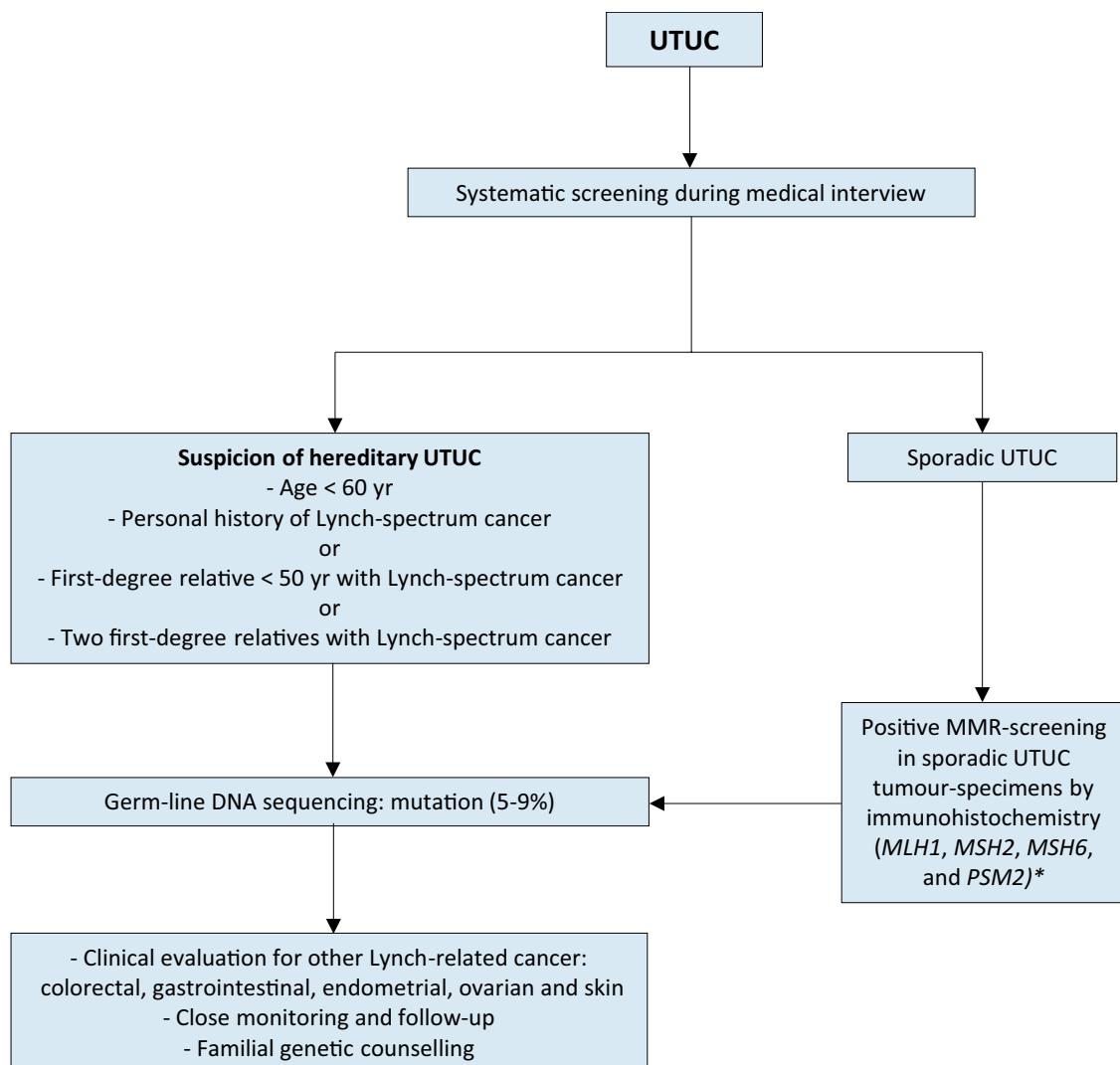
With regards to UTUC occurring following an initial diagnosis of bladder cancer, a series of 82 patients treated with bacillus Calmette-Guérin (BCG) who had regular upper tract imaging between years 1 and 3 showed a 13% incidence of UTUC, all of which were asymptomatic [17], whilst in another series of 307 patients without routine upper tract imaging the incidence was 25% [18]. 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 [19]. Following radical cystectomy for MIBC, 3–5% of patients develop a metachronous UTUC [20, 21].

Approximately two-thirds of patients who present with UTUCs have invasive disease at diagnosis compared to 15–25% of patients presenting with muscle-invasive bladder tumours [22]. This is probably due to the absence of muscularis propria layer in the upper tract, so tumours are more likely to upstage at an earlier time-point. Approximately 9% of patients present with metastasis [10, 23, 24]. Upper urinary tract UCs have a peak incidence in individuals aged 70–90 years and are twice as common in men [25].

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 [26].

The Amsterdam criteria are a set of diagnostic criteria used by doctors to help identify families which are likely to have Lynch syndrome [27]. In Lynch-related UTUC, immunohistochemistry (IHC) analysis showed loss of protein expression corresponding to the disease-predisposing MMR (mismatch repair) gene mutation in 98% of the samples (46% were microsatellite unstable and 54% microsatellite stable) [28]. The majority of tumours develop in *MSH2* mutation carriers [28]. Patients identified at high risk for Lynch syndrome should undergo DNA sequencing for patient and family counselling [29, 30]. 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 [31]. A study of 115 consecutive UTUC patients, reported that 13.9% screened positive for potential Lynch syndrome and 5.2% had confirmed Lynch syndrome [32]. This is one of the highest rates of undiagnosed genetic disease in urological cancers, which justifies screening of all patients under 60 presenting with UTUC and those with a family history of UTUC (see Figure 3.1) [33, 34] or positive reflexive MMR-test by IHC in sporadic UTUC [31, 35–37].

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



\*Sporadic UTUC that for any reason has undergone MMR screening with a positive result should test for germ-line DNA sequencing mutations.

MMR = mismatch repair; mismatch repair genes = MLH1, MSH2, MSH6, and PSM2; UTUC = upper urinary tract urothelial carcinoma.

### 3.2 Risk factors

A number of environmental factors have been implicated in the development of UTUC [12, 38]. 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 [39-41]. A large population-based study assessing familial clustering in relatives of UC patients, including 229,251 relatives of case subjects and 1,197,552 relatives of matched control subjects, has demonstrated genetic or environmental roots independent of smoking-related behaviours. With more than 9% of the cohort being UTUC patients, clustering was not seen in upper tract disease. This may suggest that the familial clustering of UC is specific to lower tract cancers [42].

In Taiwan and Chile, the presence of arsenic in drinking water has been tentatively linked to UTUC [43, 44]. Aristolochic acid, a nitrophenanthrene carboxylic acid produced by Aristolochia plants, which are used worldwide, especially in China and Taiwan [45], 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 [45-47]. Aristolochic acid has been linked to bladder cancer, renal cell carcinoma, hepatocellular carcinoma, and intrahepatic cholangiocarcinoma [48]. Two routes of exposure to aristolochic acid are known: (i) environmental contamination of agricultural products by Aristolochia plants, as reported for Balkan endemic nephropathy [49]; and (ii) ingestion of Aristolochia-

based herbal remedies [50, 51]. Following bioactivation, aristolochic acid reacts with genomic DNA to form aristolactam-deoxyadenosine adducts [52]; 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 [48, 53]. However, fewer than 10% of individuals exposed to aristolochic acid develop UTUC [47].

Two retrospective series found that aristolochic acid-associated UTUC is more common in females [54, 55]. However, females with aristolochic acid UTUC have a better prognosis than their male counterparts. Consumption of arsenic in drinking water and aristolochia-based herbal remedies together appears to have an additive carcinogenic effect [56].

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 g of alcohol/day. A dose-response was observed [57].

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 [26]. So far, two UTUC-specific polymorphisms have been reported [58].

A history of bladder cancer is associated with a higher risk of developing UTUCs (see Section 3.1). Patients who undergo ureteral stenting at the time of TURB, including prior to radical cystectomy are at higher risk for upper tract recurrence [59, 60].

### **3.3 Histology and classification**

#### **3.3.1 Histological types**

Upper urinary tract tumours are almost always UCs and pure non-urothelial histology is rare [53, 54]. However, variants are present in approximately 25% of UTUCs [55, 56]. Pure squamous cell carcinoma of the urinary tract is often assumed to be associated with chronic inflammatory diseases and infections arising from urolithiasis [57, 58]. Urothelial carcinoma with divergent squamous differentiation is present in approximately 15% of cases [57]. Keratinising squamous metaplasia of urothelium is a risk factor for squamous cell cancers and therefore mandates surveillance. Upper urinary tract UCs with variant histology are high-grade and have a worse prognosis compared with pure UC [56, 59, 60]. Other variants, although rare, include sarcomatoid and UCs with inverted growth [60].

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 [61].

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

<b>Summary of evidence</b>	<b>LE</b>
Aristolochic acid and smoking exposure increase the risk for UTUC.	2a
Patients with Lynch syndrome are at risk for UTUC.	2a

<b>Recommendations</b>	<b>Strength rating</b>
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]. However because of the difficulty in adequate sample acquisition, it is often difficult to distinguish between non-invasive papillary tumours [70], flat lesions (carcinoma *in situ* [CIS]), and invasive carcinoma. Therefore, histological grade is often used for clinical decision making as it is strongly associated with pathological stage [71].

### 4.2 Tumour Node Metastasis staging

The tumour, node, metastasis (TNM) classification is shown in Table 1 [72]. The regional lymph nodes (LN<sub>s</sub>) 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 [73, 74]. In 2016, an update of the 2004 WHO grading classification was published without major changes [73]. These guidelines are still based on both the 1973 and 2004/2016 WHO classifications since most published data use the 1973 classification [70].

**Table 1: TNM classification 2017 for upper tract urothelial cell carcinoma [72]**

T - Primary tumour	
TX	Primary tumour cannot be assessed
T0	No evidence of primary tumour
	Ta Non-invasive papillary carcinoma
	Tis Carcinoma <i>in situ</i>
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).

### 4.4 Molecular classification of UTUCs

A number of studies focussing on molecular classification have been able to demonstrate genetically distinct groups of UTUC by evaluating DNA, RNA and protein expression. Five molecular subtypes with different gene expression, tumour location and outcome have been identified, but, as yet, it is unclear whether these subtypes will respond differently to treatment [75].

## 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%) [76, 77]. Flank pain, due to clot or tumour tissue obstruction or less often due to local growth, occurs in approximately 20–32% of cases [78]. 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 [78].

## **5.2 Imaging**

### **5.2.1 Computed tomography urography**

Computed tomography (CT) urography has the highest diagnostic accuracy of the available imaging techniques [79]. A meta-analysis of 13 studies comprising 1,233 patients revealed a pooled sensitivity of CT urography for UTUC of 92% (CI: 0.85–0.96) and a pooled specificity of 95% (CI: 0.88–0.98) [80].

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 [81, 82].

### **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 [83]. The sensitivity of MR urography is 75% after contrast injection for tumours < 2 cm [83]. 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 more sensitive and specific for the diagnosis and staging of UTUC compared to MR urography [84].

## **5.3 Cystoscopy**

Urethrocytostoscopy is an integral part of UTUC diagnosis to rule out concomitant bladder cancer [10, 13].

## **5.4 Cytology**

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, 85, 86]. Cytology is less sensitive for UTUC than bladder tumours and should be performed selectively for the affected upper tract [87]. In a recent study, barbotage cytology detected up to 91% of cancers [88]. Barbotage cytology taken from the renal cavities and ureteral lumina is preferred before application of a contrast agent for retrograde ureteropyelography as it may cause deterioration of cytological specimens [89]. Retrograde ureteropyelography remains an option to detect UTUCs [79, 90, 91].

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 [92, 93].

## **5.5 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 more than 90% of cases with a low false-negative rate, regardless of sample size [94]. Undergrading may occur following diagnostic biopsy, making intensive follow-up necessary if kidney-sparing treatment is chosen [71, 95]. Ureteroscopy also facilitates selective ureteral sampling for cytology *in situ* [91, 96, 97]. 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 [97, 98]. In a meta-analysis comparing URS vs. no URS prior to RNU, 8/12 studies found an increased risk for intravesical recurrence if URS was performed before RNU [99]. Performing a biopsy at URS was also identified as a risk factor for intravesical recurrence [99].

Technical developments in flexible ureteroscopes and the use of novel imaging techniques improve visualisation and diagnosis of flat lesions [100]. Narrow-band imaging is a promising technique, but results are preliminary [101]. 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 [102, 103]. Recommendations for the diagnosis of UTUC are listed in Section 5.7.

## **5.6 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 [80]. A SEER analysis shows that approximately 9% of patients present with distant metastases [104].

### **5.6.1 $^{18}\text{F}$ -Fluorodeoxyglucose positron emission tomography/computed tomography**

A retrospective multi-centre publication on the use of  $^{18}\text{F}$ -Fluorodeoxyglucose positron emission tomography/computed tomography (FDG-PET/CT) for the detection of nodal metastasis in 117 surgically-treated UTUC patients reported a promising sensitivity and specificity of 82% and 84%, respectively. Suspicious LNs on FDG-PET/CT were associated with worse recurrence-free survival [105]. These results warrant further validation and comparison with MR urography and CT.

## 5.7 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.	2a
Selective urinary cytology has high sensitivity in high-grade tumours, including carcinoma <i>in situ</i> .	3
Urethrocystoscopy can detect concomitant bladder cancer.	2a

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 or <sup>18</sup> F-Fluorodeoxglucose positron emission tomography/CT may be used when CT is contra-indicated.	Weak

## 6. PROGNOSIS

### 6.1 Prognostic factors

Many prognostic factors have been identified and can be used to risk-stratify patients in order to decide on the most appropriate local treatment (radical vs. conservative) and discuss peri-operative systemic therapy. Factors can be divided into patient-related factors and tumour-related factors.

#### 6.1.1 Patient-related factors

##### 6.1.1.1 Age and gender

Older age at the time of RNU is independently associated with decreased cancer-specific survival (CSS) [106, 107] (LE: 3). Gender has no impact on prognosis of UTUC [108].

##### 6.1.1.2 Ethnicity

One multicentre study in academic centres did not show any difference in outcomes between races [109], 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) [14].

##### 6.1.1.3 Tobacco consumption

Being a smoker at diagnosis increases the risk for disease recurrence, mortality [110, 111] and intravesical recurrence after RNU [112] (LE: 3). There is a close relationship between tobacco consumption and prognosis [113] (LE: 3); smoking cessation improves cancer control [111].

##### 6.1.1.4 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 [114-118] (LE: 3).

##### 6.1.1.5 Other factors

Comorbidity and performance indices (e.g. American Society of Anesthesiologists [ASA], performance status [PS], and Charlson Comorbidity Index) are also associated with worse survival outcomes across disease stages [119-122].

A higher ASA score confers worse CSS after RNU [123] (LE: 3), as does poor PS [124]. Obesity and higher body mass index adversely affect cancer-specific outcomes in patients treated with RNU [125] (LE: 3), with potential differences between races [126]. Several blood-based biomarkers have been associated with locally advanced disease and cancer-specific mortality such as high pre-treatment-derived neutrophil-lymphocyte ratio [127-130], low albumin [129, 131], high C-reactive protein [129] or modified Glasgow score [132], high De Ritis ratio (aspartate transaminase/alanine transaminase) [133], altered renal function [129, 134] and high fibrinogen [129, 134] (LE: 3).

### **6.1.2 Tumour-related factors**

#### **6.1.2.1 Tumour stage and grade**

The main prognostic factors are tumour stage and grade [22, 97, 107, 135]. Upper urinary tract UCs that invade the muscle wall have a poor prognosis. In a large Dutch series of UTUC, 5-year CSS was 86% for non-muscle-invasive tumours, 70% for muscle-invasive organ-confined tumours and 44% for locally-advanced tumours [136]. A SEER contemporary analysis of RNUs for high-risk disease showed that 5-year CSS was 86% for T1N0, 77% for T2N0, 63% for T3N0 and 39% for T4N0/T any N1-3 [137].

#### **6.1.2.2 Tumour location, multifocality, size and hydronephrosis**

Initial location of the UTUC is a prognostic factor in some studies [138, 139] (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 [140-145]. Hydronephrosis is associated with advanced disease and poor oncological outcome [81, 89, 146]. Increasing tumour size is associated with a higher risk of muscle-invasive and/or non-organ-confined disease, both in ureteral and renal pelvis UTUC. A large multi-institutional retrospective study including 932 RNUs performed for non-metastatic UTUC demonstrated that 2 cm appears to be the best cut-off in identifying patients at risk of harbouring  $\geq$  pT2 UTUC [147]. In a SEER database analysis of 4,657 patients with renal pelvis UTUC, each gain of 1 cm in tumour size was associated with a 1.25-fold higher risk of pT2-T4 histology at RNU [104].

#### **6.1.2.3 Variant histology**

Pathological variants are associated with worse cancer-specific and overall survival (OS) [64] (LE: 3). Most studied variants are micropapillary [67], squamous [148] and sarcomatoid [67] which are consistently associated with locally-advanced disease and worse outcome.

#### **6.1.2.4 Lymph node involvement**

Patients with nodal metastasis experience very poor survival after surgery [149]. Lymph node density (cut-off 30%) and extranodal extension are powerful predictors of survival outcomes in N+ UTUC [150-152]. Lymph node dissection (LND) performed at the time of RNU allows for optimal tumour staging, although its curative role remains controversial [151, 153-155] (LE: 3).

#### **6.1.2.5 Lymphovascular invasion**

Lymphovascular invasion (LVI) is present in approximately 20% of invasive UTUCs and is an independent predictor of survival [156-158]. Lymphovascular invasion status should be specifically reported in the pathological reports of all UTUC specimens [156, 159, 160] (LE: 3).

#### **6.1.2.6 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 [161] (LE: 3).

#### **6.1.2.7 Other pathological factors**

Extensive tumour necrosis ( $> 10\%$  of the tumour area) is an independent prognostic predictor in patients who undergo RNU [162, 163] (LE: 3). In case neoadjuvant treatment was administered, pathological downstaging is associated with better OS [164, 165] (LE: 3). The architecture of UTUC, as determined from pathological examination of RNU specimens, is also a strong prognosticator with sessile growth pattern being associated with worse outcome [166-168] (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 [169, 170] (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 [63, 171].

### **6.1.3 Molecular markers**

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 investigated markers have been validated yet to support their introduction in daily clinical decision making [140, 172].

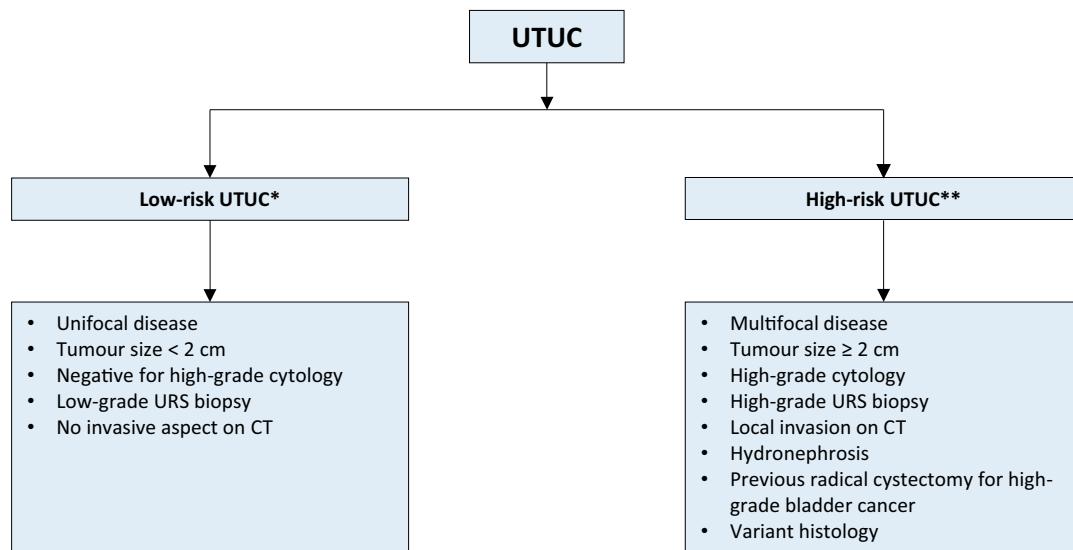
## **6.2 Risk stratification for clinical decision making**

### **6.2.1 Low- versus high-risk UTUC**

As tumour stage is difficult to assess clinically in UTUC, it is useful to “risk stratify” UTUC between low- and high risk of progression to identify those patients who are more likely to benefit from kidney-sparing treatment and those who should be treated radically [173, 174] (see Figure 6.2). The factors to consider for risk stratification are presented in Figure 6.1.

Several new risk stratification models have been assessed to improve upon the dichotomous EAU risk grouping, with the main aim to avoid overtreatment (i.e., better stratify patients eligible for kidney-sparing surgery). Examples include multivariable models with novel clinical characteristics [175] a tumour grade-and stage-based model [176] and a three-tier risk stratification model (i.e., low-, intermediate-, and high risk) [177]. These models need further validation.

**Figure 6.1: Risk stratification of non-metastatic UTUC**



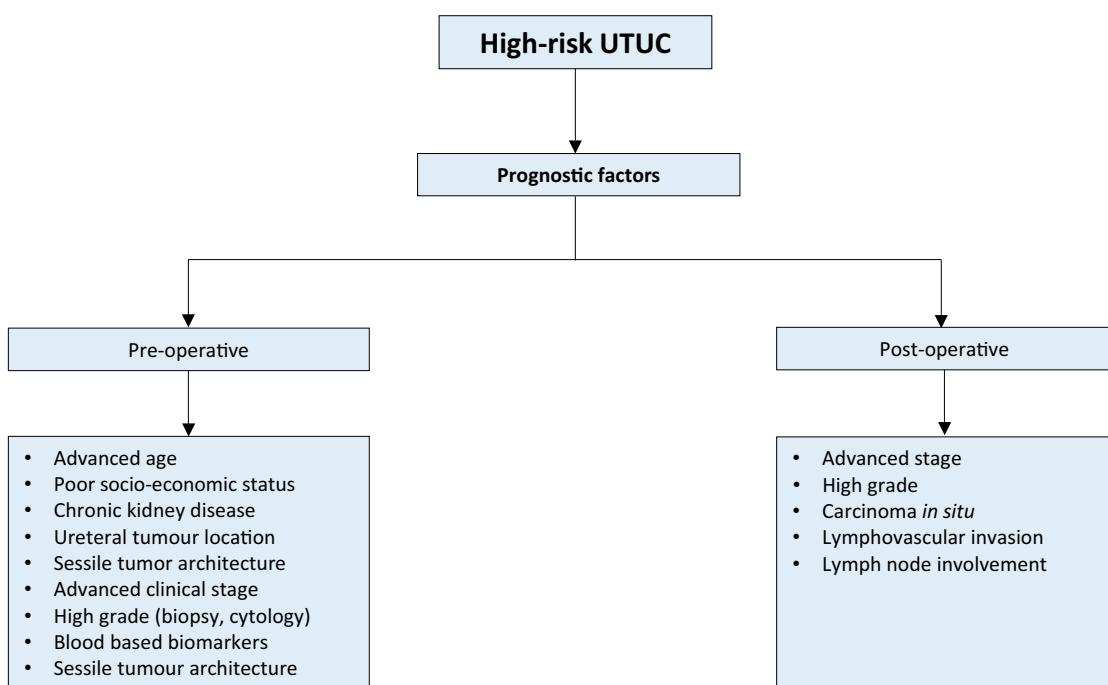
\* All these factors need to be present.

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

#### 6.2.2 Peri-operative predictive tools for high-risk disease

There are several pre-RNU models aiming at predicting which patient has muscle-invasive/non-organ-confined disease [162, 178-181] (LE: 3). Prognostic nomograms based on pre-operative factors and post-operative pathological characteristics are available [153, 180, 182-187]. The main factors included in these models, which may be used when counselling patients regarding follow-up and administration of peri-operative chemotherapy, are detailed in Figure 6.2.

**Figure 6.2: UTUC prognostic factors included in prognostic models**



*UTUC = upper tract urothelial carcinoma.*

## 6.3 Bladder recurrence

A meta-analysis of available data has identified significant predictors of bladder recurrence after RNU [188] (LE: 3). Three categories of predictors for increased risk of 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, tumour grade, ureteral location, multifocality, tumour diameter, invasive pT stage, and necrosis [189].
3. Treatment-specific factors such as laparoscopic approach, extravesical bladder cuff removal, and positive surgical margins [188].

In addition, the use of diagnostic URS has been associated with a higher risk of developing bladder recurrence after RNU [190, 191] (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 [188].

## 6.4 Summary of evidence and guidelines for the prognosis of UTUC

Summary of evidence	LE
Important prognostic factors for risk stratification include tumour multifocality, size, stage, grade, hydronephrosis and variant histology.	3
Models are available to predict non-organ-confined disease and altered prognosis after RNU.	3
Patient, tumour, and treatment-related factors impact the risk of bladder recurrence.	3
Currently, no prognostic biomarkers are validated for clinical use.	3

Recommendation	Strength rating
Use prognostic 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 [192]. In low-risk cancers, it is the preferred approach as survival is similar to that after RNU [192]. 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 selected high-risk 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 [193, 194]. A flexible ureteroscope is useful in the management of pelvicalyceal tumours [195]. The patient should be informed of the need and be willing to comply with an early second-look URS [196] and stringent surveillance; complete tumour resection or destruction is necessary [196]. 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 [197].

#### 7.1.1.2 Percutaneous access

Percutaneous management can be considered for low-risk UTUC in the renal pelvis [193, 198] (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 [194, 198]. Moreover, a risk of tumour seeding remains with a percutaneous access [198].

#### 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 [192]. Segmental resection of the proximal two-thirds of ureter is associated with higher failure rates than for the distal ureter [199, 200] (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 (in case of an imperative indication) [183, 199, 201] (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 [202].

#### 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 [170, 203] (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 [204-207].

A 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 endocavitory 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 upper tract CIS, finding no difference between the method of drug administration (antegrade vs. retrograde vs. combined approach) in terms of recurrence, progression, CSS, and OS. Furthermore, the recurrence rates following adjuvant instillations are comparable to those reported in the literature in untreated patients, questioning their efficacy [208]. The analyses were based on retrospective small studies suffering from publication and reporting bias.

Recent evidence suggests that early single adjuvant intracavitary instillation of mitomycin C in patients with low-grade UTUC might reduce the risk of local recurrence [209] (LE: 3). This needs to be confirmed in further studies. The authors report limited complications related to the instillations, but propose a retrograde pyelography before instillations are commenced to exclude contrast extravasation. This concept will need further evaluation in a randomised context [209].

A single-arm phase III trial showed that the use of mitomycin-containing reverse thermal gel (UGN-101) instillations in a chemoablation setting via retrograde catheter to the renal pelvis and calyces was associated with a complete response rate in a total of 42 patients (59%) with biopsy-proven low-grade UTUC measuring less than 15 mm. The most frequently reported all-cause adverse events were ureteric stenosis in 31 (44%) of 71 patients, urinary tract infection in 23 (32%), haematuria in 22 (31%), flank pain in 21 (30%), and nausea in 17 (24%). A total of 19 (27%) of 71 patients had drug-related or procedure-related serious adverse events. No deaths were regarded as related to treatment [210].

#### 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 (distal ureterectomy) 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 in consultation 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 [22] (LE: 3). Radical nephroureterectomy must be performed according to oncological principles preventing tumour seeding [22]. 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 [211, 212]. 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 [213, 214].

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 [212, 215-218] (LE: 3). One prospective randomised study has shown that laparoscopic RNU is inferior to open RNU for non-organ-confined UTUC. However, this was a small trial ( $n = 80$ ), which was likely underpowered [214] (LE: 2). Oncological outcomes after RNU have not changed significantly over the past three decades despite staging and surgical refinements [219] (LE: 3). In a population-based data set, a hospital volume of  $\geq 6$  patients per year treated with RNU showed improvement of short-term outcomes (30- and 90-day mortality) and overall long-term survival [220]. A robot-assisted laparoscopic approach can be considered with recent data suggesting oncologic equivalence with the other approaches [221-223].

#### 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 [188, 199, 224-226]. 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 [16, 224, 225] (LE: 3).

#### 7.1.2.1.4 Lymph node dissection

The use of a LND template is likely to have a greater impact on patient survival than the number of removed LNs [227]. Template-based and completeness of LND improves CSS in patients with muscle-invasive disease and reduces the risk of local recurrence [228]. Even in clinically [229] and pathologically [230] node-negative patients, LND improves survival. The risk of LN metastasis increases with advancing tumour stage [154]. Lymph node dissection appears to be unnecessary in cases of TaT1 UTUC because of the low risk of LN metastasis [231-234], however, tumour staging is inaccurate pre-operatively; therefore a template-based LND should be offered to all patients who are scheduled for RNU for high-risk non-metastatic UTUC. The templates for LND have been described [228, 235, 236].

### 7.1.3 Peri-operative chemotherapy

#### 7.1.3.1 Neoadjuvant chemotherapy

In patients treated prior to losing their renal reserve several retrospective studies evaluating the role of neoadjuvant chemotherapy have shown promising pathological downstaging and complete response rates [164, 237-240]. No RCTs have been published yet but prospective data from a phase II trial showed that the use of neoadjuvant chemotherapy was associated with a 14% pathological complete response rate for high-grade UTUC [241]. In addition, final pathological stage was  $\leq$  ypT1 in more than 60% of included patients with acceptable toxicity profile. In a systematic review and meta-analysis comprising more than 800 patients, neoadjuvant chemotherapy has shown a pathologic partial response of 43% and a downstaging in 33% of patients, and also an OS and CSS survival benefit compared with RNU alone [242]. Furthermore, neoadjuvant chemotherapy has been shown to result in lower disease recurrence and mortality rates compared to RNU alone without compromising the use of definitive surgical treatment [239, 243-245].

#### 7.1.3.2 Adjuvant chemotherapy

##### 7.1.3.2.1 Chemotherapy

A phase III prospective randomised trial ( $n = 261$ ) evaluating the benefit of adjuvant gemcitabine-platinum combination chemotherapy initiated within 90 days after RNU vs. surveillance has reported a significant improvement in disease-free survival in patients with pT2-pT4, N (any) or LN-positive (pT any, N1-3) M0 UTUC [246] (LE: 1).

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 [247, 248]. In a retrospective study histological variants of UTUC exhibit different survival rates and adjuvant chemotherapy was only associated with an OS benefit in patients with pure UC [249] (LE: 3).

#### 7.1.3.2.2 Immunotherapy

In a phase 3, multicentre, double-blind RCT involving patients with high-risk muscle-invasive UC who had undergone radical surgery, adjuvant nivolumab improved disease-free survival compared to placebo in the intention-to-treat population (20.8 vs 10.8 months) and among patients with a PD-L1 expression level of 1% or more [250]. The median survival free from recurrence outside the urothelial tract in the intention-to-treat population was 22.9 months with nivolumab and 13.7 months with placebo. Treatment-related adverse events ≥ grade 3 occurred in 17.9% of the nivolumab group and 7.2% of the placebo group. The subgroup of patients with UTUC in this study needs further analysis to better understand the effect of adjuvant nivolumab for high-risk muscle-invasive UC after RNU.

#### 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 [251-254]. Moreover, its added value to chemotherapy remains questionable [253].

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

The rate of bladder recurrence after RNU for UTUC is 22–47% [174, 224]. Two prospective randomised trials [255, 256] and two meta-analyses [257, 258] 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 drug extravasation.

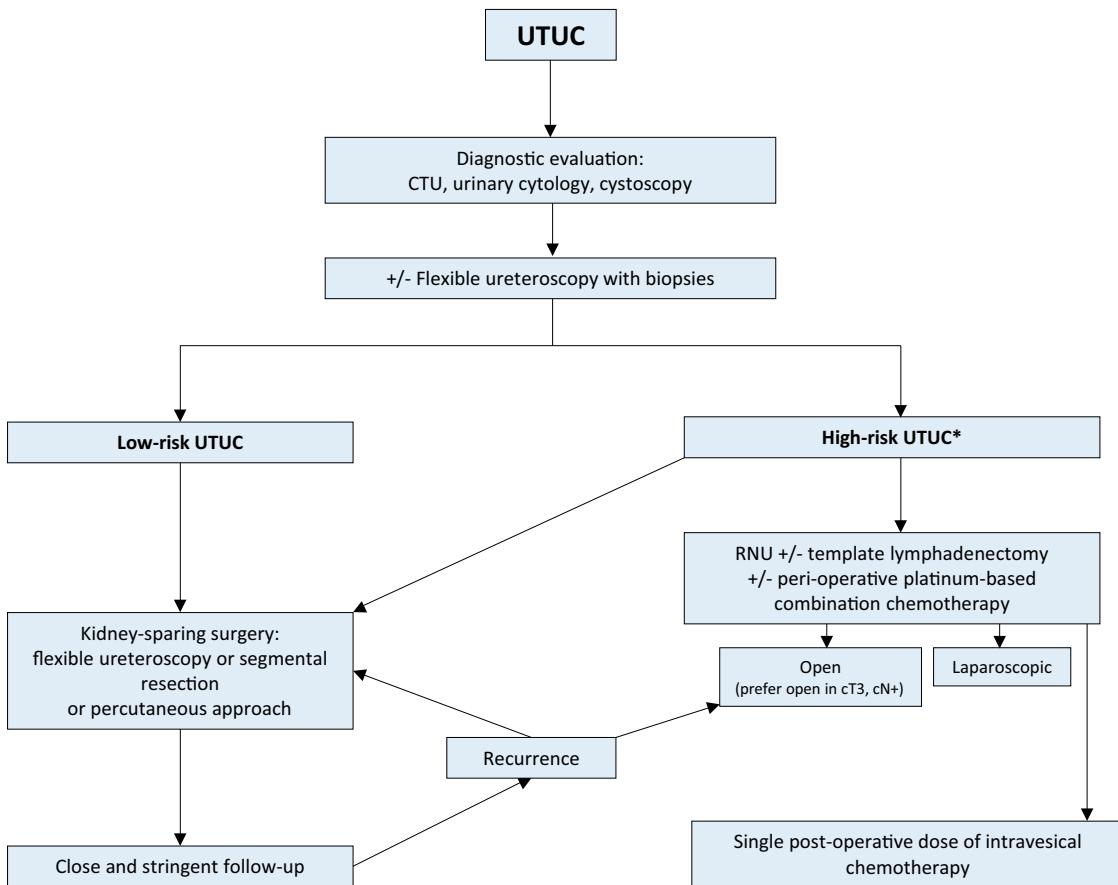
Based on current evidence it is unlikely that additional instillations beyond one peri-operative instillation of chemotherapy further substantially reduces the risk of intravesical recurrence [259]. Whilst there is no direct evidence supporting the use of intravesical instillation of chemotherapy after 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. One low-level evidence study suggested that bladder irrigation might reduce the risk of bladder recurrence after RNU [260].

#### 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.	2a
Open, laparoscopic and robotic approaches have similar oncological outcomes for organ-confined UTUC.	2a
Failure to completely remove the bladder cuff increases the risk of bladder cancer recurrence.	3
Lymphadenectomy improves survival in muscle-invasive UTUC.	3
Post-operative chemotherapy improves disease-free survival.	1b
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
Perform a template-based lymphadenectomy in patients with high-risk non-metastatic UTUC.	Strong
Offer post-operative systemic platinum-based chemotherapy to patients with high-risk non-metastatic UTUC.	Strong
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**

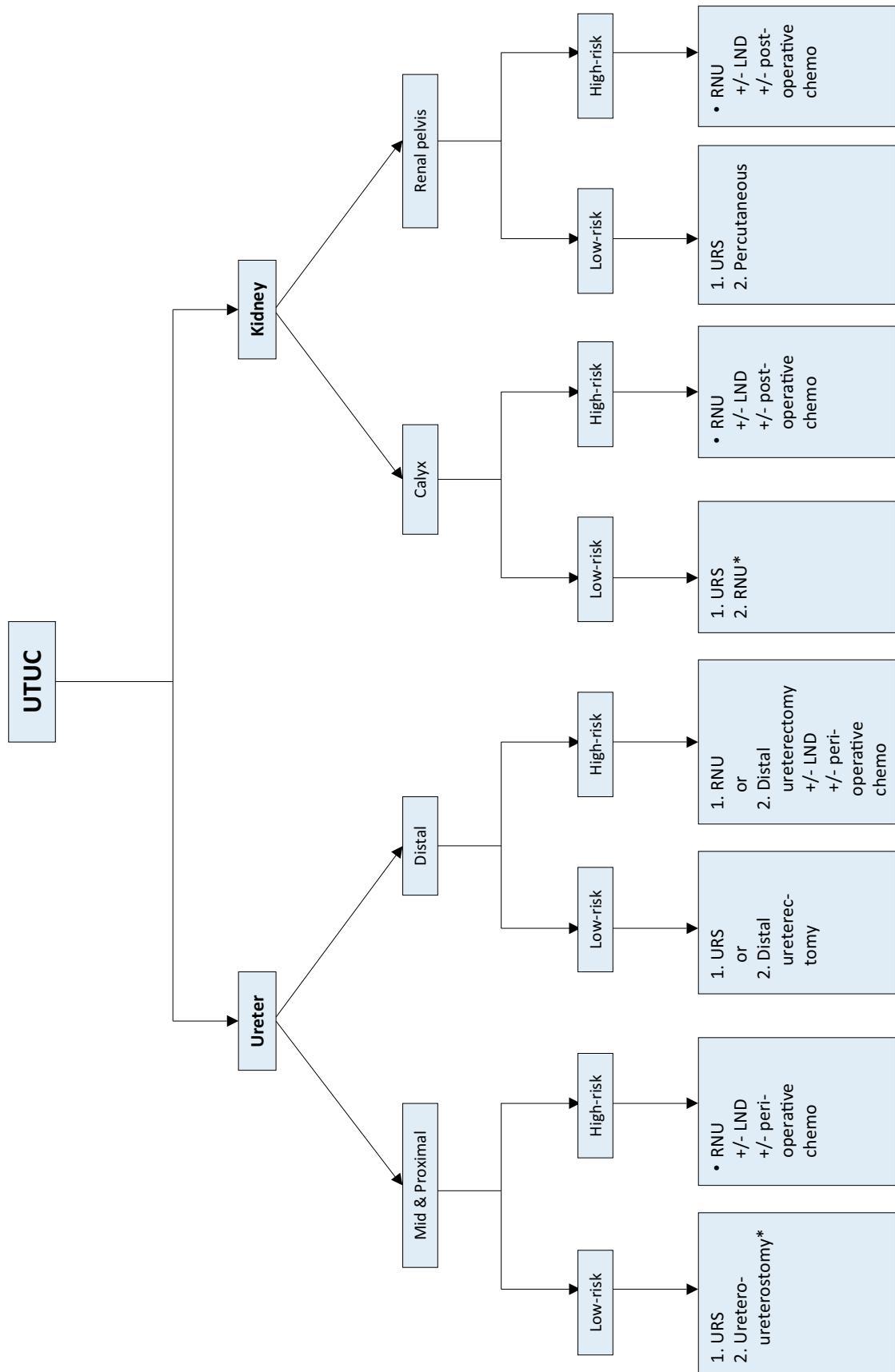


\*In patients with solitary kidney, consider a more conservative approach.

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 [261-264]. Although evidence remains very limited, RNU may be associated with cancer-specific [261, 263, 264] and OS benefit in selected patients, especially those fit enough to receive cisplatin-based chemotherapy [262, 263]. It is noteworthy that these benefits may be limited to those patients with only one metastatic site [263]. 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 [18, 110] (LE: 3).

### **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 6 months [265-267]. This was confirmed in the most recent and largest study to date [268]. In patients with metastases limited to lung and/or lymph nodes, whose disease responded to systemic chemotherapy, metastasectomy can improve oncological outcomes in individual cases [269] (LE: 3).

Nonetheless, in the absence of data from RCTs, patients should be evaluated on an individual basis and the decision to perform a metastasectomy (surgically) should be made following a shared decision-making process with the patient.

### **7.2.3 Systemic treatments**

#### **7.2.3.1 First-line setting**

##### **7.2.3.1.1 Patients fit enough to tolerate cisplatin-based combination chemotherapy**

Data from the bladder cancer literature and from small, single-centre UTUC studies suggest that platinum-based combination chemotherapy, especially cisplatin, is efficacious as first-line treatment of metastatic UTUC. Cisplatin-containing combination chemotherapy is standard in advanced or metastatic patients fit enough to tolerate cisplatin [2]. A number of cisplatin-containing chemotherapy regimens are acceptable although gemcitabine and cisplatin is the most widely used. A retrospective analysis of three RCTs showed that primary tumour location in the lower- or upper urinary tract had no impact on progression-free survival (PFS) or OS in patients with locally advanced or metastatic UC treated with platinum-based combination chemotherapy [270]. The efficacy of immunotherapy using programmed death-1 (PD1) or programmed death-ligand 1 (PD-L1) inhibitors has been evaluated in the first-line setting for the treatment of cisplatin-fit patients with metastatic UC, including those with UTUC [271]. The combination of platinum-based chemotherapy with immune checkpoint inhibitors have not resulted in positive significant survival advantages and are not currently recommended [272].

##### **7.2.3.1.2 Patients fit for carboplatin (but unfit for cisplatin-based combination chemotherapy)**

Carboplatin-based chemotherapy is recommended in patients unfit for cisplatin [2]. Carboplatin with gemcitabine is the preferred regimen [273].

##### **7.2.3.1.3 Maintenance therapy after first-line platinum-based treatment**

Platinum-based chemotherapy followed by maintenance avelumab is preferred to upfront immune checkpoint inhibitors in both PD-L1 biomarker positive and negative patients. Data from a phase III RCT showed that the use of avelumab maintenance therapy after 4 to 6 cycles of gemcitabine plus cisplatin or carboplatin (started within 10 weeks of completion of first-line platinum-based chemotherapy) significantly prolonged OS as compared to best supportive care alone in those patients with advanced or metastatic UC who did not progress during, or responded to, first-line chemotherapy (HR 0.69; 95% CI 0.56–0.86) [274, 275]. An increase in median OS from 14 to 21 months was observed with avelumab. Although no subgroup analysis based on tumour location was available in this study, almost 30% of the included patients had UTUC. Similarly, in a phase II study comprising 108 patients with metastatic UC achieving at least stable disease on first-line platinum-based chemotherapy, maintenance pembrolizumab improved PFS compared to placebo (5.4 vs. 3.0 months) [276].

##### **7.2.3.1.4 Immunotherapy in cisplatin-unfit patients**

Pembrolizumab or atezolizumab are alternative choices for patients who are PD-L1 positive and not eligible for cisplatin-based chemotherapy, although RCTs failed to show significant superiority compared with chemotherapy [272, 277]. Final data from randomised trials with durvalumab are similar with no OS benefit [278]. Biomarkers (SP142 for atezolizumab; 22C3 for pembrolizumab) should be used to match the drug, as recommended by the European Medicines Agency (EMA) [279, 280].

In a single-arm phase II trial ( $n = 370$ ) of cisplatin-ineligible UC, pembrolizumab monotherapy was

associated with an objective response rate of 26% in 69 metastatic UTUC patients [281]. In the overall cohort, a PD-L1 expression of 10% was associated with a greater response rate to pembrolizumab. Treatment-related toxicity was in line with previous studies. In a single-arm phase II trial ( $n = 119$ ) of cisplatin-ineligible UC, atezolizumab monotherapy was associated with an objective response rate of 39% in 33 (28%) metastatic UTUC patients [282]. Median OS in the overall cohort was 15.9 months and treatment-related toxicity was in line with previous studies. Data from a phase III RCT including 1,213 patients with metastatic cisplatin-eligible and cisplatin-ineligible UC, of which 312 (26%) were diagnosed with UTUC, showed that the combination of atezolizumab with platinum-based chemotherapy prolonged both PFS and OS [277]. No subgroup analysis based on tumour location was performed in this study.

#### 7.2.3.2 Second-line setting

##### 7.2.3.2.1 Immunotherapy

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 compared to second-line chemotherapy (the investigator's choice of paclitaxel, docetaxel, or vinflunine); median OS: 10.3 months for pembrolizumab and 7.4 months for chemotherapy, HR 0.73, 95% CI: 0.59–0.91 [283]. Responses were more frequent and durable for pembrolizumab compared with chemotherapy (21% vs. 11%). In the UTUC subgroup ( $n = 75$ , 13.8%), the OS benefit seemed larger (50%).

The IMVigor211 trial explored atezolizumab in PD-L1 biomarker positive tumours in patients with tumours which have relapsed after platinum-based therapy and failed to show a significant OS advantage [284].

In a phase II study, 48 patients with platinum-refractory UC (18/48 patients with UTUC) were treated with cabozantinib. There was one complete response and 7 partial responses (objective response rate 19%, 95% CI: 9–34). Median PFS was 3.7 months (95% CI: 3–6) [285].

Other immunotherapies such as nivolumab [286], avelumab [287, 288] and durvalumab [289] have shown objective response rates ranging from 17.8% [289] to 19.6% [286] and median OS ranging from 7.7 months to 18.2 months in patients with platinum-resistant metastatic UC. 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 for avelumab ( $n = 7/15.9\%$ ) without any subgroup analysis based on primary tumour location [288].

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 [290]. 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 [291].

##### 7.2.3.2.2 Novel agents

###### *Fibroblast growth factor receptors (FGFR) inhibition*

Erdafitinib, a pan-FGFR tyrosine kinase inhibitor of FGFR1–4, was associated with a 40% response rate in a phase II trial in 99 patients with locally advanced or metastatic UC who progressed after first-line chemotherapy and harboured a FGFR DNA genomic alterations (FGFR2 or 3 mutations, or FGFR3 fusions) [292]. This study included 23 UTUC patients with visceral metastases showing a 43% response rate.

###### *Antibody drug conjugates (ADC)*

A phase II study enrolled 89 patients (of whom 43% had UTUC) with metastatic UC progressing after therapy with PD-1 or PD-L1 inhibitors. All patients received the antibody-drug conjugate enfortumab vedotin. The objective response rate was 52%, 20% of patients achieved complete response [293].

#### 7.2.3.3 Third-line setting

In an open-label phase II trial a total of 108 patients with metastatic UC with progression on platinum-based and checkpoint inhibitors were treated with the antibody-drug conjugate sacituzumab govitecan. The objective response rate was 27%, with median duration of response 7.2 months, median PFS 5.4 months and OS 10.9 months. The site of primary UC is not mentioned in the publication [294].

A pre-planned subgroup analysis from the phase III RANGE trial assessed the impact on outcomes and safety of ramucirumab added to docetaxel after disease progression on both platinum and immune checkpoint inhibitors therapy [295]. Median PFS was 3.15 months on ramucirumab/docetaxel vs 2.73 months on placebo/docetaxel (HR = 0.786, 95%, CI: 0.404–1.528,  $p = 0.4877$ ). This trend for ramucirumab benefit occurred despite the ramucirumab arm having a higher percentage of patients with poorer prognosis. However, these findings need confirmation by further studies, as this analysis is limited by patient numbers and an imbalance in the treatment arms.

## 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
Cisplatin-containing combination chemotherapy is standard in advanced or metastatic patients fit enough to tolerate cisplatin.	1b
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
Maintenance avelumab is associated with an OS advantage compared with best supportive care in patients who did not have disease progression after 4 to 6 cycles of gemcitabine plus cisplatin or carboplatin.	1b
PD-1 inhibitor pembrolizumab has been approved for patients who have progressed during or after previous platinum-based chemotherapy and did not receive previous immune therapy based on the results of a phase III trial.	1b
PD-L1 inhibitor atezolizumab has been approved for patients that have progressed during or after previous platinum-based chemotherapy and did not receive previous immune therapy 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 and did not receive previous immune therapy 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
Erdafitinib improves OS in in platinum-refractory patients with locally advanced or metastatic UC and FGFR DNA genomic alterations ( <i>FGFR2</i> or 3 mutations, or <i>FGFR3</i> fusions).	2a

Recommendations	Strength rating
Offer radical nephroureterectomy as a palliative treatment to symptomatic patients with resectable locally advanced tumours.	Weak
<b>First-line treatment for cisplatin-eligible patients</b>	
Use cisplatin-containing combination chemotherapy with GC or HD-MVAC.	Strong
Do not offer carboplatin or non-platinum combination chemotherapy.	Strong
Use maintenance avelumab in patients who did not have disease progression after 4 to 6 cycles of gemcitabine plus cisplatin.	Strong
<b>First-line treatment in patients unfit for cisplatin</b>	
Offer checkpoint inhibitors pembrolizumab or atezolizumab depending on PD-L1 status.	Weak
Offer carboplatin combination chemotherapy if PD-L1 is negative.	Strong
Use maintenance avelumab in patients who did not have disease progression after 4 to 6 cycles of gemcitabine plus carboplatin.	Strong
<b>Second-line treatment</b>	
Offer checkpoint inhibitor (pembrolizumab) to patients with disease progression during or after platinum-based combination chemotherapy for metastatic disease.	Strong
Offer checkpoint inhibitor (atezolizumab or nivolumab) to patients with disease progression during or after platinum-based combination chemotherapy for metastatic disease.	Strong
Offer erdafitinib in platinum-refractory tumours with FGFR alterations.	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-line treatment.	Strong

GC = gemcitabine plus cisplatin; FGFR = fibroblast growth factor receptors; HD-MVAC = high-dose intensity 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 [296]. A direct relationship exists between event-free follow-up and survival probability after RNU [137]. Stringent follow-up is mandatory to detect metachronous bladder tumours (probability increases over time [297]), local recurrence, and distant metastases.

Surveillance regimens are based on cystoscopy and urinary cytology [15, 297]. Bladder recurrence is not considered a distant recurrence. When kidney-sparing surgery is performed, the ipsilateral UUT requires careful and long-term follow-up due to the high risk of disease recurrence [195, 298, 299] and progression to RNU beyond 5 years [300]. Despite endourological improvements, follow-up after kidney-sparing management is difficult and frequent, and repeated endoscopic procedures are necessary. Following kidney-sparing surgery, and as done in bladder cancer, an early repeated (second look) ureteroscopy within 6 to 8 weeks after primary endoscopic treatment has been proposed, but is not yet routine practice [2, 196]. Section 8.1 presents the summary of evidence and recommendations for follow-up of UTUC.

### 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
<b>After radical nephroureterectomy</b>	
<i>Low-risk tumours</i>	
Perform cystoscopy at three months. If negative, perform subsequent cystoscopy 9 months later and then yearly, for 5 years.	Weak
<i>High-risk tumours</i>	
Perform cystoscopy and urinary cytology at 3 months. If negative, repeat subsequent cystoscopy and cytology every 3 months for a period of 2 years, and every 6 months thereafter until 5 years, and then yearly.	Weak
Perform computed tomography (CT) urography and chest CT every 6 months for 2 years, and then yearly.	Weak
<b>After kidney-sparing management</b>	
<i>Low-risk tumours</i>	
Perform cystoscopy and CT urography at 3 and 6 months, and then yearly for 5 years.	Weak
Perform ureteroscopy (URS) at 3 months.	Weak
<i>High-risk tumours</i>	
Perform cystoscopy, urinary cytology, CT urography and chest CT at 3 and 6 months, and then yearly.	Weak
Perform URS and urinary cytology <i>in situ</i> at 3 and 6 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 available on 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

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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