

# 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 clinicians with evidence-based information and recommendations for the management of upper urinary tract urothelial carcinoma (UTUC). Separate EAU guidelines 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 presenting the main findings of the UTUC Guidelines. This is an abridged version 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 2021 [4]. All documents are accessible through the EAU website: <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 2023 publication presents a limited update of the 2022 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 2023 print can be found in:

- Section 5.7 Summary of evidence and recommendations for the diagnosis of UTUC, the following recommendations were revised:

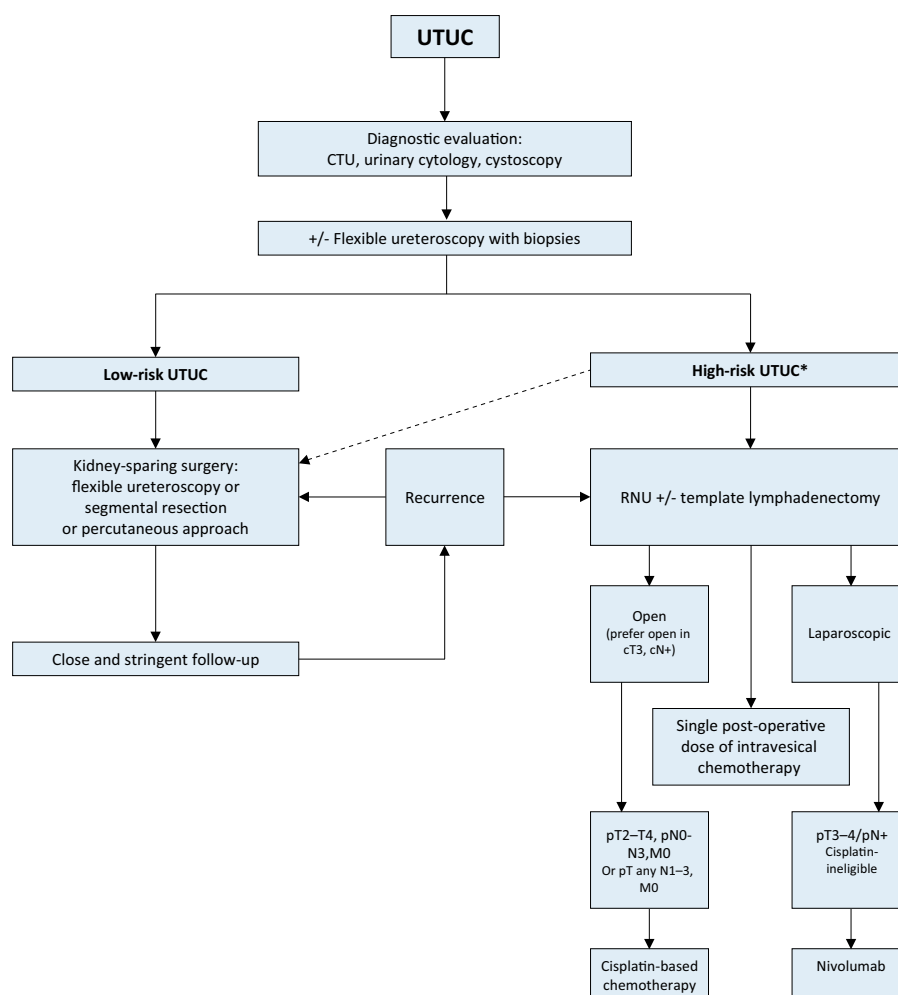
Recommendations	Strength rating
2022 recommendation: Use diagnostic ureteroscopy and biopsy if imaging and cytology are not sufficient for the diagnosis and/or risk-stratification of the tumour.	Strong
Revised 2023 recommendation: Use diagnostic ureteroscopy (preferably without biopsy) if imaging and/or voided urine cytology are not sufficient for the diagnosis and/or risk-stratification of patients suspected to have UTUC.	Strong
2022 recommendation: Magnetic resonance urography or <sup>18</sup> F-Fluorodeoxyglucose positron emission tomography/CT may be used when CT is contra-indicated.	Weak
Revised 2023 recommendation: Magnetic resonance urography or <sup>18</sup> F-Fluorodeoxyglucose positron emission tomography/CT (to assess [nodal] metastasis) may be used when CT is contra-indicated.	Weak

- Chapter 7 Disease Management has been restructured resulting in recommendations moved to other sections and new recommendations having been added to Section 7.2.5 Summary of evidence and guidelines for the management of high-risk non-metastatic UTUC:

Summary of evidence	LE
Post-operative platinum-based adjuvant chemotherapy improves disease-free survival.	1b

Recommendations	Strength rating
New 2023 recommendation: Offer adjuvant platinum-based chemotherapy after RNU to patients with pT2–T4 and/or pN+ disease.	Strong
New 2023 recommendation: Discuss adjuvant nivolumab with patients unfit for, or who declined, platinum-based adjuvant chemotherapy for ≥ pT3 and/or pN+ disease after RNU alone or ≥ ypT2 and/or ypN+ disease after neoadjuvant chemotherapy, followed by RNU.	Weak
2022 recommendation: 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
Revised 2023 recommendation: Offer kidney-sparing management to high-risk patients with imperative indication on a case-by-case basis, in consultation with the patient.	Strong

- New data prompted changes to Figure 7.1 Proposed flowchart for the management of UTUC.



- Section 7.3.3 Summary of evidence and recommendations for the treatment of metastatic UTUC:

Summary of evidence	LE
Carboplatin-based combination chemotherapy offers a survival benefit in cisplatin unfit patients.	1b

Erdafitinib was associated with radiological response in platinum-refractory patients with locally-advanced or metastatic UC and <i>FGFR</i> DNA genomic alterations ( <i>FGFR2/3</i> mutations or <i>FGFR3</i> fusions).	2a
Enfortumab vedotin was associated with OS benefit in patients who had previously received platinum-containing chemotherapy and experienced disease progression during or after treatment with a PD-1 or PD-L1 inhibitor.	1b
Palliative nephroureterectomy can improve quality of life by controlling symptomatic disease.	3
RNU can confer a survival benefit in highly selected patients.	4

Recommendations	Strength rating
<b>First-line treatment for cisplatin-eligible patients</b>	
New 2023 recommendation: Offer platinum combination chemotherapy to platinum-eligible patients.	Strong
<b>First-line treatment in patients ineligible for cisplatin or carboplatin</b>	
New 2023 recommendation: Offer gemcitabine/carboplatin chemotherapy to cisplatin-ineligible patients.	Strong
2022 recommendation: Offer checkpoint inhibitors pembrolizumab or atezolizumab depending on PD-L1 status.	Weak
Revised 2023 recommendation: Offer checkpoint inhibitors pembrolizumab or atezolizumab to patients with PD-L1 positive tumours.	Weak
<b>Second-line treatment</b>	
New 2023 recommendation: Offer enfortumab vedotin to patients previously treated with platinum-containing chemotherapy and who had disease progression during or after treatment with a PD-1 or PD-L1 inhibitor.	Strong
2022 recommendation: Offer erdafitinib in platinum-refractory tumours with <i>FGFR</i> alterations.	Strong
Revised 2023 recommendation: Offer erdafitinib as subsequent-line therapy to platinum-refractory patients with <i>FGFR</i> DNA genomic alterations ( <i>FGFR2/3</i> mutations or <i>FGFR3</i> fusions).	Weak

DNA = deoxyribonucleic acid; *FGFR* = fibroblast growth factor receptors; PD-L1 = programmed death ligand 1.

- Section 8.1 Summary of evidence and recommendations for the follow-up of UTUC:

Recommendations	Strength rating
<b>After kidney-sparing management</b>	
<b>Low-risk tumours</b>	
2022 recommendation: Perform ureteroscopy (URS) at 3 months.	Weak
Revised 2023 recommendation: Perform ureteroscopy (URS) at 3 months if no second-look ureteroscopy was performed.	Weak

## 2. METHODS

### 2.1 Data identification

Standard procedure for EAU Guidelines includes an annual assessment of newly published literature in the field to guide future updates. For the 2023 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 8<sup>th</sup> 2021 and May 4<sup>th</sup> 2022. 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 319 unique records were identified, retrieved, and screened for relevance.

Excluded from the search were basic research studies, case series, reports, and editorial comments. 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 33 new publications were included in the 2023 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 which includes the assessment of the benefit to harms ratio and patients' preferences for each recommendation. The strength rating forms draws on the guiding principles of the GRADE methodology but do not purport to be GRADE [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 2023 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 localised 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 (BC) 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 BC is present [13] whilst a prior history of BC 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]. A retrospective international registry including data from 2,380 patients from 2014 to 2019 (101 centres in 29 countries) confirmed that UTUC patients were predominantly male (70.5%) and 53.3% were past or present smokers. The majority of patients (58.1%) were evaluated because of symptoms, mainly visible haematuria [17]. The latter was confirmed by a meta-analysis pooling 44 studies and showing a pooled incidence rate for UTUC of 0.75% for visible haematuria and 0.17% for nonvisible haematuria [18].

With regards to UTUC occurring following an initial diagnosis of BC, a series of 82 patients treated with bacillus Calmette-Guérin (BCG) who had regular upper tract imaging between years 1 and 3 showed a

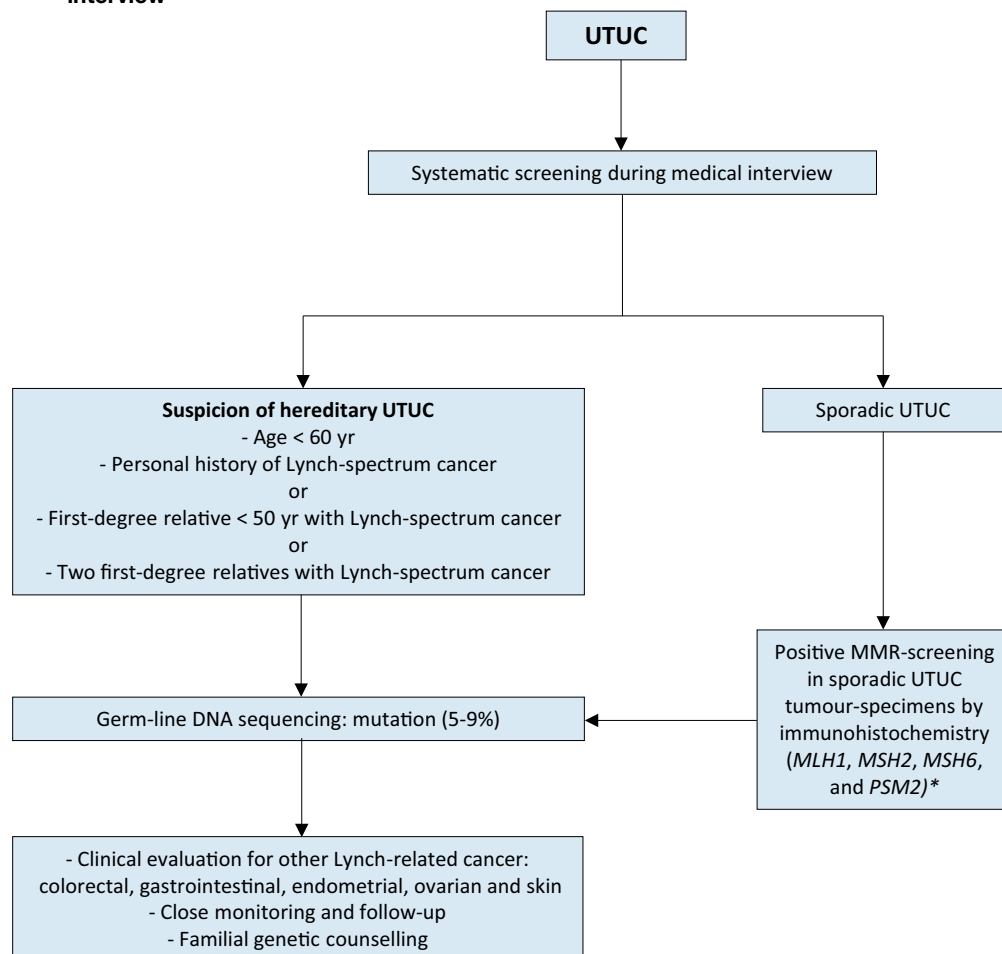
13% incidence of UTUC, all of which were asymptomatic [19], whilst in another series of 307 patients without routine upper tract imaging the incidence was 25% [20]. A multicentre cohort study (n = 402) with a 50 month follow-up demonstrated a UTUC incidence of 7.5% in NMIBC patients receiving BCG with predictors being intravesical recurrence and non-papillary tumour at transurethral resection of the bladder (TURB) [21]. Following radical cystectomy for MIBC, 3–5% of patients develop a metachronous UTUC [22, 23].

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 [24]. 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, 25–27]. Upper urinary tract UCs have a peak incidence in individuals aged 70–90 years and are twice as common in men [28].

Upper tract UC and BC exhibit significant differences in the prevalence of common genomic alterations. In individual patients with a history of both tumours, BC and UTUC are often clonally related. Genomic characterisation of UTUC provides information regarding the risk of bladder recurrence and can identify tumours associated with Lynch syndrome [29].

The Amsterdam criteria are a set of diagnostic criteria to help identify families which are likely to have Lynch syndrome [30]. 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 instable and 54% microsatellite stable) [31]. The majority of tumours develop in *MSH2* and *MSH6* mutation carriers [31]. Patients identified at high risk for Lynch syndrome should undergo germline DNA sequencing for patient and family counselling [32, 33]. Germline mutations in DNA MMR genes defining Lynch syndrome are found in 9% of patients with UTUC compared to 1% of patients with BC, linking UTUC to Lynch syndrome [34]. A study of 115 consecutive UTUC patients, reported that 13.9% screened positive for potential Lynch syndrome and 5.2% had confirmed Lynch syndrome [35]. 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) [36, 37] or positive reflexive MMR-test by IHC in sporadic UTUC [34, 38–41].

**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 prompt subsequent testing for germline 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, 42]. 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 [43–45]. 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 [46].

In Taiwan and Chile, the presence of arsenic in drinking water has been tentatively linked to UTUC [47, 48].

Aristolochic acid, a nitrophenanthrene carboxylic acid produced by aristolochia plants, which are used worldwide, especially in China and Taiwan [49], 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 [49–51]. Aristolochic acid has been linked to BC, renal cell carcinoma, hepatocellular carcinoma, and intrahepatic cholangiocarcinoma [52]. Two routes of exposure to aristolochic acid are known: (i) environmental contamination of agricultural products by aristolochia plants, as reported for Balkan endemic nephropathy [53]; and (ii) ingestion of aristolochia-based herbal remedies [54, 55]. Following bioactivation, aristolochic acid reacts with genomic DNA to form aristolactam-deoxyadenosine adducts [56]; 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 [52, 57]. However, fewer than 10% of individuals exposed to aristolochic acid develop UTUC [51].

Two retrospective series found that aristolochic acid-associated UTUC is more common in females [58, 59]. 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 [60].

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 [61].

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 [29]. So far, two UTUC-specific polymorphisms have been reported [62].

A history of BC is associated with a higher risk of developing UTUCs (see Section 3.1). Patients requiring ureteral stenting at the time of TURB, including prior to radical cystectomy, have been shown to have a higher risk for upper tract recurrence [63, 64].

### 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 [65, 66]. However, histological subtypes are present in approximately 25% of UTUCs [67, 68]. Pure squamous cell carcinoma of the urinary tract is often assumed to be associated with chronic inflammatory diseases and infections arising from urolithiasis [69, 70]. Urothelial carcinoma with divergent squamous differentiation is present in approximately 15% of cases [69]. Keratinising squamous metaplasia of urothelium is a risk factor for squamous cell cancers and therefore mandates surveillance. Upper urinary tract UCs with different subtypes are high-grade and have a worse prognosis compared with pure UC [68, 71, 72]. Other subtypes, although rare, include sarcomatoid and UCs with inverted growth [72].

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 [73].

### 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.	2a
Patients with Lynch syndrome are at risk for UTUC.	2a

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]. However because of the difficulty in adequate sample acquisition, it is often difficult to distinguish between non-invasive papillary tumours [74], 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 [75].

### 4.2 Tumour Node Metastasis staging

The tumour, node, metastasis (TNM) classification is shown in Table 1 [76]. 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 and 2016, 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 [77, 78]. In 2022, an update of the 2004/2016 WHO grading classification was published without major changes [79]. These guidelines are still based on both the 1973 and 2004/2016 WHO classifications since most published data use the 1973 classification [74].

**Table 1: TNM classification 2017 for upper tract urothelial cell carcinoma [76]**

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 different 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 and therefore, these subtypes have limited use in daily practice [80].

## 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%) [81, 82]. However, the pooled incidence rate in a systematic review of 44 studies assessing haematuria for the presence of UTUC, was only 0.75% (95% CI: 0.4–1.2%) for visible haematuria and 0.17% (95% CI: 0.081–0.299%) for nonvisible haematuria [18]. Flank pain, due to clot or tumour tissue obstruction or less often due to local growth, occurs in approximately 20–32% of cases [17]. 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 [17].

### 5.2 Imaging

#### 5.2.1 Computed tomography urography

Computed tomography (CT) urography has the highest diagnostic accuracy of the available imaging techniques [83]. 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) [84].

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 [85, 86].

#### 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 [87]. The sensitivity of MR urography is 75% after contrast injection for tumours < 2 cm [87]. Computed tomography urography is more sensitive and specific for the diagnosis and staging of UTUC compared to MR urography [88].

#### 5.2.3 <sup>18</sup>F-Fluorodeoxyglucose positron emission tomography/computed tomography

A retrospective multicentre publication on the use of <sup>18</sup>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 [89]. These results warrant further validation and comparison with MR urography and CT. FDG-PET/CT can also be used to assess (nodal) metastasis in patients unfit for iodinated contrast media due to renal impairment or allergy.

### 5.3 Cystoscopy

Urethrocystoscopy is an integral part of UTUC diagnosis to rule out concomitant BC [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, 90, 91]. Cytology is less sensitive for UTUC than bladder tumours and should be performed selectively for the affected upper tract [92]. In a recent study, barbotage cytology detected up to 91% of cancers [93]. 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 [94]. Retrograde ureteropyelography remains an option to detect UTUCs [75, 95, 96]. The sensitivity of fluorescence *in situ* hybridisation (FISH) for molecular abnormalities characteristic of UTUCs is approximately 72–84% [97, 98]. A prospective study in 82 patients with a suspicion of UTUC using upper tract urine collected just before URS, reported sensitivities for Xpert Bladder, FISH and cytology of 100%, 93% and 52%, respectively. Negative predictive values were 100%, 96% and 81%, respectively [99]. These promising results suggest that URS might be avoided in selected patients with a positive urine biomarker test. However, further confirmation in comparative trials will be needed.

## 5.5 Diagnostic ureteroscopy

Flexible ureteroscopy (URS) is used to confirm the diagnosis of UTUC by visualising the ureter, renal pelvis and collecting system and perform a biopsy of suspicious lesions. It is also essential for meticulous tumour mapping before considering kidney-sparing options for UTUC. Presence, appearance, multifocality and size of the 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 [100]. However, undergrading occurs with ureteroscopic diagnostic biopsy compared to nephroureterectomy specimens [101], making intensive follow-up necessary if kidney-sparing treatment is chosen [75, 102].

Ureteroscopy also facilitates selective ureteral sampling for cytology *in situ* [96, 103, 104]. Stage assessment using ureteroscopic biopsy can be 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 [104, 105]. 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 [106]. Performing a biopsy at URS was also identified as a risk factor for intravesical recurrence [106]. A second systematic review of 16 studies showed that URS alone was not significantly related to intravesical recurrence; whereas URS with a biopsy significantly increased the risk for subsequent intravesical recurrence albeit with no concurrent impact on (long-term) survival outcomes [107]. This underlines the need for a study evaluating an immediate intravesical instillation in patients who underwent URS plus biopsy, or laser treatment, for UTUC.

Technical developments in flexible ureteroscopes and the use of novel imaging techniques may improve visualisation and diagnosis of flat lesions [108]. Narrow-band imaging is a promising technique, but results are preliminary [109]. 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 [110, 111]. 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 [84]. A SEER analysis showed that approximately 9% of patients present with distant metastases [112].

## 5.7 Summary of evidence and recommendations 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 BC.	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 (preferably without biopsy) if imaging and/or voided urine cytology are not sufficient for the diagnosis and/or risk-stratification of patients suspected to have UTUC.	Strong
Magnetic resonance urography or <sup>18</sup> F-Fluorodeoxyglucose positron emission tomography/CT (to assess [nodal] metastasis) 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) [113, 114] (LE: 3). Gender has no impact on prognosis of UTUC [115].

#### 6.1.1.2 *Ethnicity*

One multicentre study in academic centres did not show any difference in outcomes between races [116], 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 factors, disease characteristics and predictors of adverse oncologic outcomes) [14].

#### 6.1.1.3 *Genetic pre-disposition*

Patients who test positive for Lynch syndrome, based on IHC (MSI testing all 4 markers) [117].

#### 6.1.1.4 *Tobacco consumption*

Being a smoker at diagnosis increases the risk for disease recurrence, mortality [118, 119] and intravesical recurrence after RNU [120] (LE: 3). There is a close relationship between tobacco consumption and prognosis [121] (LE: 3); smoking cessation improves cancer control [119].

#### 6.1.1.5 *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 [122-126] (LE: 3).

#### 6.1.1.6 *Other factors*

High comorbidity and performance indices scores (e.g. American Society of Anesthesiologists [ASA], performance status [PS], and Charlson Comorbidity Index) are also associated with worse survival outcomes across disease stages [127-130].

A higher ASA score confers worse CSS after RNU [131] (LE: 3), as does poor PS [132]. Obesity and higher body mass index adversely affect cancer-specific outcomes in patients treated with RNU [133] (LE: 3), with potential differences between races [134]. Several blood-based biomarkers have been associated with locally-advanced disease and cancer-specific mortality such as high pre-treatment-derived neutrophil-lymphocyte ratio [135-138], low albumin [137, 139], high C-reactive protein [137] or modified Glasgow score [140], high De Ritis ratio (aspartate transaminase/alanine transaminase) [141], altered renal function [137, 142] and high fibrinogen [137, 142] (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 [24, 104, 114, 143]. 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 [27]. A contemporary SEER 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 [144]. pT3 sub staging (pT3a vs. pT3b) might be relevant [145].

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

Initial location of the UTUC is a prognostic factor in some studies [146, 147] (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 [148-153]. Hydronephrosis is associated with advanced disease and poor oncological outcome [85, 94, 154]. 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 > pT2 UTUC [155]. 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 [112].

#### 6.1.2.3 *Pathological subtypes*

Pathological subtypes are associated with worse CSS and overall survival (OS) [68] (LE: 3). Most studied subtypes are micropapillary [71], squamous [156] and sarcomatoid [71], all of 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 [157]. Lymph node density (cut-off 30%) and extranodal extension are powerful predictors of survival outcomes in N+ UTUC [158-160]. Lymph node dissection (LND) performed at the time of RNU allows for optimal tumour staging, although its curative role remains controversial [159, 161-163] (LE: 3). Patients with clinically N+ UTUC should be offered chemotherapy, with surgery offered after a good response.

#### 6.1.2.5 *Lymphovascular invasion*

Lymphovascular invasion (LVI) is present in approximately 20% of invasive UTUCs and is an independent predictor of survival [164-166]. Lymphovascular invasion status should be specifically reported in the pathological reports of all UTUC specimens [167, 168] (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 [169] (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 [170, 171] (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 [172-174] (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 [175, 176] (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 [67, 177].

#### 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 [148, 178].

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

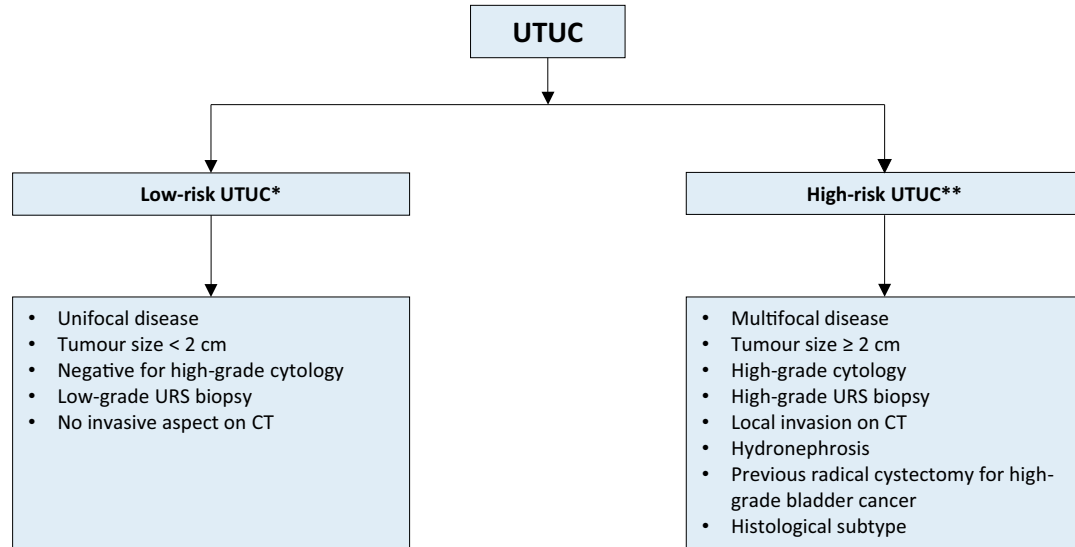
As tumour stage is difficult to assess clinically in UTUC, pre-RNU models aiming at predicting which patient has  $\geq$  pT2 /non-organ-confined disease have been published [179-183] (LE: 3). Several risk stratification models have been assessed with the main aim to better stratify patients eligible for kidney-sparing surgery [184-188].

Prognostic nomograms based on pre-operative factors and post-operative pathological characteristics are also available [161, 181, 189-194] and may be used when counselling patients regarding follow-up and administration of peri-operative chemotherapy.

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 [184, 185]. The factors to consider for risk stratification are presented in Figure 6.1.



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



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

\* All these factors need to be present.

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

### 6.3 Bladder recurrence

A meta-analysis of available data has identified significant predictors of bladder recurrence after RNU [195] (LE: 3). Three categories of predictors for increased risk of bladder recurrence were identified:

1. Patient-specific factors such as male gender, previous BC, 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 [196, 197].
3. Treatment-specific factors such as laparoscopic approach, extravesical bladder cuff removal, and positive surgical margins [195].

In addition, the use of diagnostic URS has been associated with a higher risk of developing bladder recurrence after RNU [198, 199] (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 [195].

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

Summary of evidence	LE
Important prognostic factors for risk stratification include tumour size, stage, grade, hydronephrosis and different histological subtypes.	3
Models are available to predict pT2/non-organ confined disease and altered prognosis after RNU.	3
Patient, tumour, and treatment-related factors impact 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 low-risk disease

#### 7.1.1 *General considerations on 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 [200]. In low-risk cancers, it is the preferred approach as survival is similar to that after RNU [200]. This option should therefore be discussed in all low-risk cases, irrespective of the status of the contralateral kidney. Recommendations for kidney-sparing management of UTUC are listed in Section 7.1.7.

#### 7.1.2 *Ureteroscopy*

Endoscopic ablation should be considered in patients with clinically low-risk cancer [201, 202]. A flexible ureteroscope is useful in the management of pelvicalyceal tumours [203]. The patient should be informed of the need and be willing to comply with an early second-look URS [204] and stringent surveillance; complete tumour resection or destruction is necessary [204]. 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 [205].

#### 7.1.3 *Percutaneous access*

Percutaneous management can be considered for low-risk UTUC in the renal pelvis [201, 206] (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 [202, 206]. Moreover, a risk of tumour seeding remains with percutaneous access [206].

#### 7.1.4 *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 [200]. Segmental resection of the proximal two-thirds of ureter is associated with higher failure rates than for the distal ureter [207, 208] (LE: 3).

Distal ureterectomy with ureteroneocystostomy are indicated for low-risk tumours in the distal ureter that cannot be removed completely endoscopically [190, 207, 209] (LE: 3). A total ureterectomy with an ileal-ureteral substitution or renal autotransplantation with pyelocystostomy is technically feasible, but only in selected cases when a renal-sparing procedure is mandatory and the tumour is low risk [210, 211].

#### 7.1.5 *Chemo-ablation*

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. Fifty-six percent of patients remained in complete response after 12 months with Kaplan-Meier analysis of durability estimated as 82% [212]. 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 [213].

#### 7.1.6 *Adjuvant instillations*

##### 7.1.6.1 *Upper urinary tract*

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 [176, 214] (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 [215-218].

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 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 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 [219]. The analyses were based on retrospective small studies suffering from publication and reporting bias.

Recent evidence suggests that early single adjuvant intracavitary upper tract instillation of mitomycin C in patients with low-grade UTUC might reduce the risk of local recurrence [220] (LE: 3). 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 [220].

#### 7.1.6.2 Bladder

There is currently no data to support the use of bladder instillation of chemotherapy after kidney-sparing surgery as available RCTs included only patients who received RNU.

### 7.1.7 Recommendation for kidney-sparing management of localised low-risk UTUC

Recommendation	Strength rating
Offer kidney-sparing management as primary treatment option to patients with low-risk tumours.	Strong

## 7.2 Localised high-risk disease

### 7.2.1 Radical nephroureterectomy

#### 7.2.1.1 Surgical approach

##### 7.2.1.1.1 Open radical nephroureterectomy

Open RNU with bladder cuff excision is the standard treatment of high-risk UTUC, regardless of tumour location [24] (LE: 3). Radical nephroureterectomy must be performed according to oncological principles preventing tumour seeding [24]. Section 7.2.5 lists the recommendations for RNU.

##### 7.2.1.1.2 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 [221, 222]. Several precautions may lower the risk of tumour spillage:

1. avoid entering the urinary tract, except when performing a bladder cuff excision and only after prior clipping of the ureter and complete drainage of the bladder;
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. in invasive or large (T3/T4 and/or N+/M+) tumours an open approach is favoured, as the oncological outcomes may be better as compared to minimally-invasive RNU [223, 224].

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 [222, 225-228] (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) [224] (LE: 2). Oncological outcomes after RNU have not changed significantly over the past three decades despite staging and surgical refinements [229] (LE: 3). In a population-based data set, a hospital volume of > 6 patients per year treated with RNU showed improvement of short-term outcomes (30- and 90-day mortality) and overall long-term survival [230]. A robot-assisted laparoscopic approach can be considered with recent data suggesting oncologic equivalence with the other approaches [231-233]. In addition, robotic RNU can limit the risk of post-operative complication with shorter length of stay as compared to the laparoscopic approach [234].

##### 7.2.1.1.3 Bladder cuff management

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 [195, 207, 235-237]. 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, 235, 236] (LE: 3).

#### 7.2.1.1.4 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 [238]. Template-based and completeness of LND improves CSS in patients with muscle-invasive disease and reduces the risk of local recurrence [239]. Even in clinically [240] and pathologically [241] node-negative patients, LND improves survival. The risk of LN metastasis increases with advancing tumour stage [162]. Lymph node dissection appears to be unnecessary in cases of TaT1 UTUC because of the low risk of LN metastasis [242-245], 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 [239, 246, 247].

#### 7.2.2 **Distal ureterectomy**

Distal ureterectomy for high-risk UTUC may be associated with similar oncological outcomes as compared to RNU [200]. This procedure can also provide the opportunity to perform a concomitant LN dissection. However, only selected cases of high-risk patients with distal ureter UTUC can benefit from this procedure, given the low level of evidence.

#### 7.2.3 **Kidney-sparing surgery for imperative indications**

Kidney-sparing surgery, including ureteroscopy or segmental ureterectomy, can be considered on a case-by-case basis for high-risk patients with imperative indications such as solitary kidney, bilateral UTUC, chronic kidney disease or any other comorbidity compromising the use of RNU (LE: 3). However, there is a greater risk of progression after kidney-sparing surgery for high- vs. low-risk UTUC with a direct impact on survival [200].

#### 7.2.4 **Peri-operative chemotherapy**

##### 7.2.4.1 **Neoadjuvant treatments**

##### 7.2.4.1.1 Chemotherapy

The primary advantage of neoadjuvant chemotherapy (NAC) is the ability to give cisplatin-based regimens when patients still have maximal renal function. Several retrospective studies evaluating the role of NAC have shown evidence of pathological downstaging and complete response rates at RNU [170, 248-251] with a direct impact on OS [183]. Furthermore, NAC has been shown to result in lower disease recurrence- and mortality rates compared to RNU alone, without compromising the use of definitive surgical treatment with a potential OS benefit [250, 252-254].

No RCTs have been published yet but prospective data from a phase II trial showed that the use of NAC was associated with a 14% pathological complete response rate in high-grade UTUC [255]. In addition, final pathological stage was < ypT1 in more than 60% of included patients with acceptable toxicity profile. In a systematic review and meta-analysis comprising more than 800 patients, NAC 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 [256]. However, it is important to note that the evidence presented above is not conclusive, given the significant bias and heterogeneity of the available data.

##### 7.2.4.1.2 Immunotherapy

Only a small phase II study including 10 patients with high-risk UTUC evaluated the efficacy of pembrolizumab in the neoadjuvant setting [257]. However, no pathological response was observed and one treatment-related death was reported. Thus, there is currently no evidence to support the use of neoadjuvant immunotherapy for high-risk UTUC.

##### 7.2.4.2 **Adjuvant treatments**

##### 7.2.4.2.1 Bladder instillations

The rate of bladder recurrence after RNU for UTUC is 22–47% [185, 235]. Two prospective randomised trials [258, 259] and two meta-analyses [260, 261] 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. All studies showed a very low risk of adverse events. Intravesical chemotherapy has also been safely given at the time of RNU, obviating the need for a post-operative cystogram, but with low level data for efficacy [262].

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 [263]. 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 [264].

#### 7.2.4.2.2 Chemotherapy

A phase III multicentre prospective RCT (n = 261) evaluating the benefit of four cycles of adjuvant gemcitabine-platinum combination chemotherapy initiated within 90 days after RNU vs. surveillance has reported a significant improvement in disease-free survival (DFS) in patients with pT2–pT4, N (any) or LN-positive (pT any, N1–3) M0 UTUC [265] (LE: 1). Patients were stratified to gemcitabine/cisplatin or gemcitabine/carboplatin chemotherapy based on GFR alone.

The main potential limitation of using adjuvant chemotherapy is the concern that renal function may deteriorate after RNU. However, fractionated cisplatin may be considered to a GFR of 45 mL/min. The initial Galsky criteria defining cisplatin eligibility (including GFR  $\geq$  60 mL/min) are not routinely used outside of clinical trials across institutions [266, 267]. In a retrospective study histological subtypes of UTUC exhibit different survival rates and adjuvant chemotherapy was only associated with an OS benefit in patients with pure UC [268] (LE: 3). However, whilst histological subtypes of UTUC exhibit different survival rates in retrospective studies, adjuvant chemotherapy should be considered where UC is the dominant pathology.

#### 7.2.4.2.3 Immunotherapy

In a phase III, multicentre, double-blind RCT involving patients with high-risk muscle-invasive UC who had undergone radical surgery, adjuvant nivolumab improved DFS compared to placebo in the intention-to-treat population (20.8 vs. 10.8 months) and among patients with a programmed death-ligand 1 (PD-L1) expression level of 1% or more [269]. The patient population predominantly consisted of BC patients post-cystectomy, with an additional smaller cohort of patients with UTUC post-RNU. The median recurrence-free survival outside the urothelial tract in the entire intention-to-treat population was 22.9 months for nivolumab and 13.7 months for placebo. Treatment-related adverse events  $\geq$  grade 3 occurred in 17.9% of the nivolumab group and 7.2% of the placebo group. On subgroup analysis, patients with UTUC included in this study did not seem to benefit from adjuvant nivolumab, which requires further follow-up and analysis.

The European Medicines Agency (EMA) approved nivolumab as monotherapy for the adjuvant treatment of patients with muscle-invasive UC with tumour cell PD-L1 expression  $\geq$  1%, who are at high risk of recurrence after undergoing radical surgery [270].

A network meta-analysis suggests superior oncological benefit for adjuvant platinum-based chemotherapy over immune checkpoint inhibitors in patients treated with radical surgery for UTUC [271].

#### 7.2.4.2.4 Radiotherapy

Adjuvant radiation therapy has been suggested to control loco-regional disease after surgical removal. The data remains controversial and insufficient for conclusions [272–275]. Moreover, its added value to chemotherapy remains questionable [274].

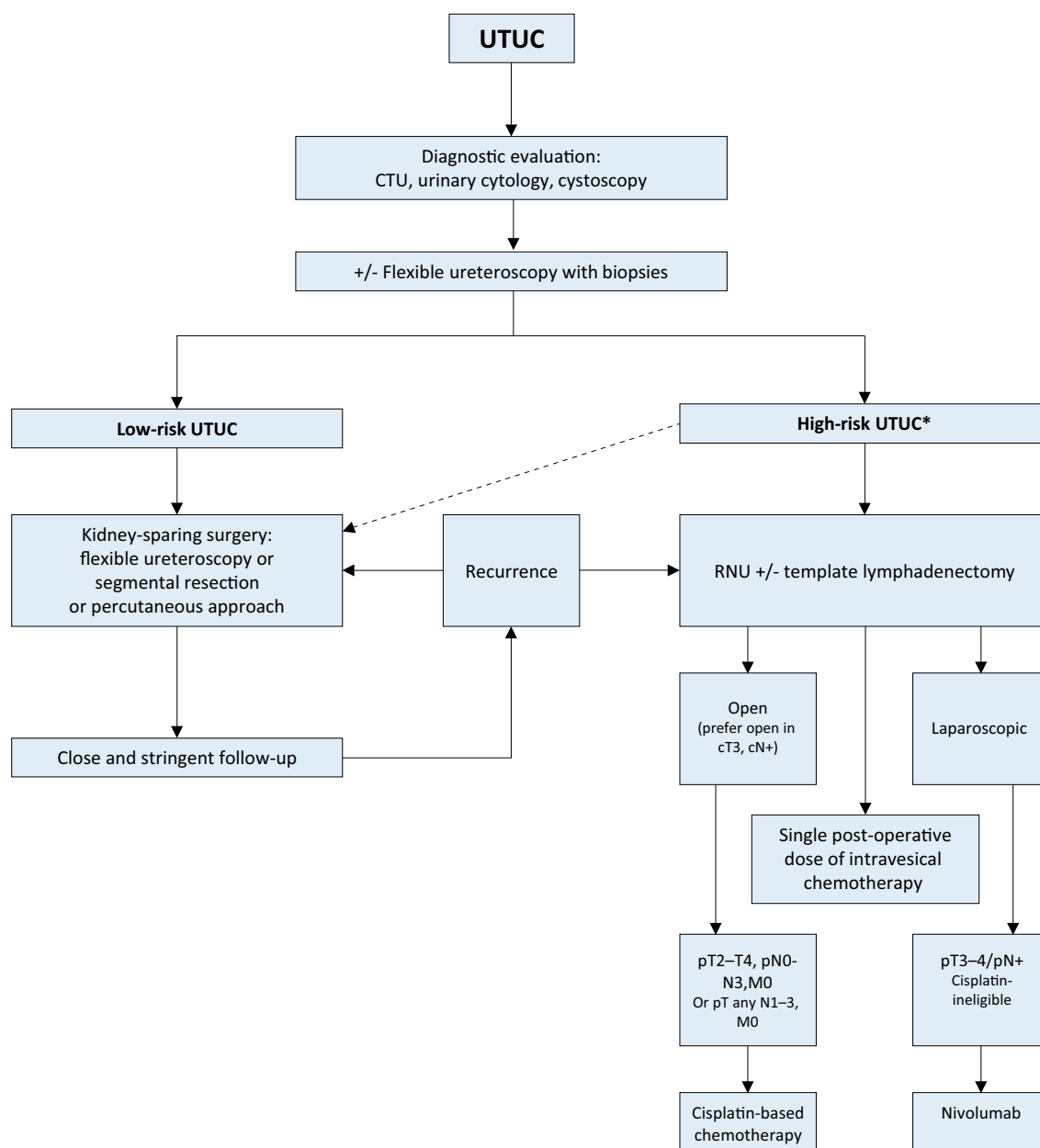
### 7.2.5 **Summary of evidence and recommendations for the management of high-risk non-metastatic UTUC**

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 BC recurrence.	3
Lymphadenectomy improves survival in muscle-invasive UTUC.	3
Post-operative platinum-based adjuvant chemotherapy improves disease-free survival.	1b
Single post-operative intravesical instillation of chemotherapy lowers the BC recurrence rate.	1b

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.	Weak

Offer adjuvant platinum-based chemotherapy after RNU to patients with pT2–T4 and/or pN+ disease.	Strong
Deliver a post-operative bladder instillation of chemotherapy to lower the intravesical recurrence rate.	Strong
Discuss adjuvant nivolumab with patients unfit for, or who declined, platinum-based adjuvant chemotherapy for $\geq$ pT3 and/or pN+ disease after RNU alone or $\geq$ ypT2 and/or ypN+ disease after neoadjuvant chemotherapy, followed by RNU.	Weak
Offer distal ureterectomy to selected patients with high-risk tumours limited to the distal ureter.	Weak
Offer kidney-sparing management to high-risk patients with imperative indication on a case-by-case basis, in consultation with the patient.	Strong

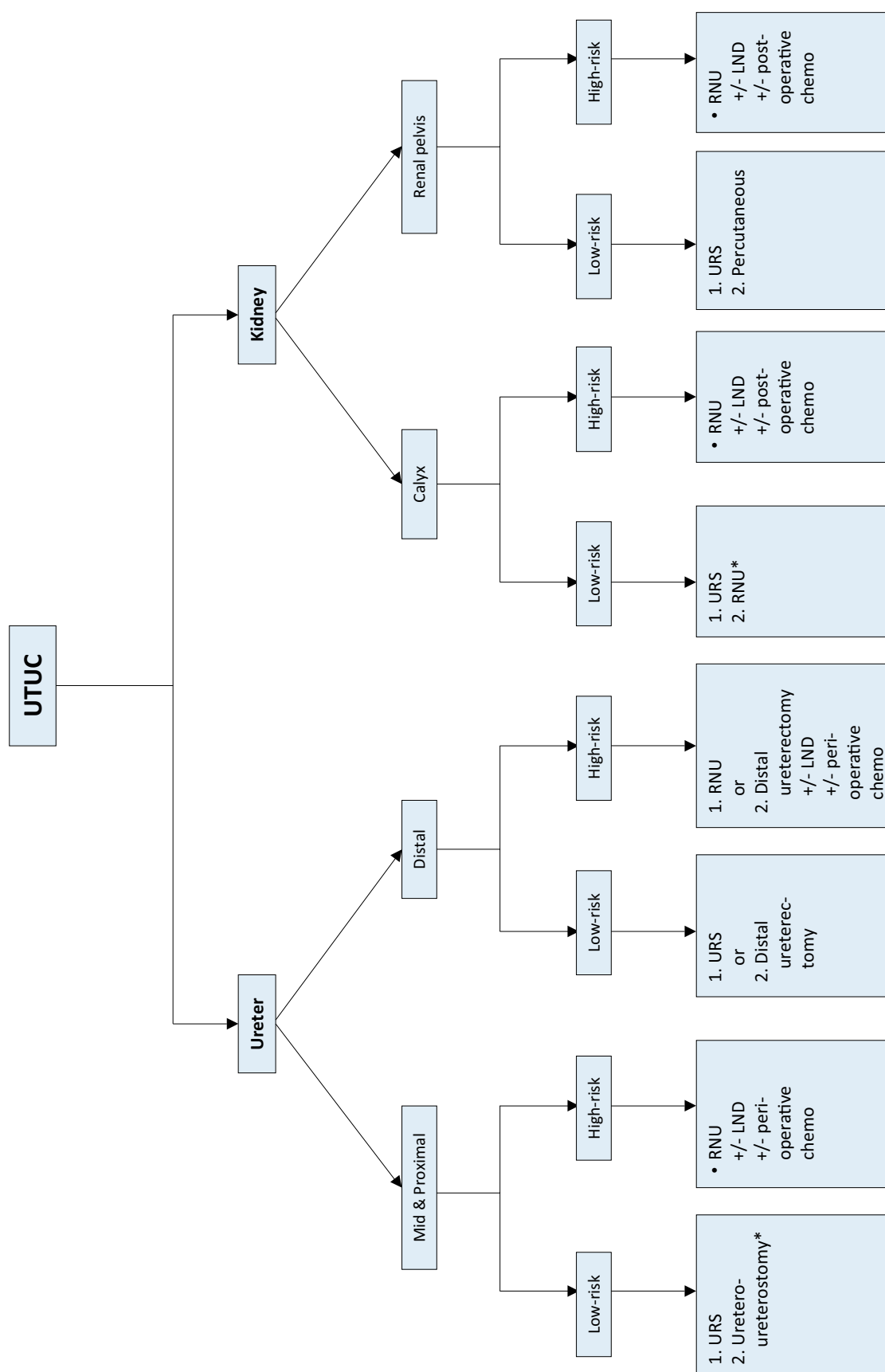
**Figure 7.1: Proposed flowchart for the management of UTUC**



*\*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 amenable to endoscopic management.

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

## 7.3 Metastatic disease

### 7.3.1 *Clinical loco-regional lymph node metastases*

Evidence is lacking regarding the optimal management of clinical node-positive disease. Patients with clinically N+ UTUC should be offered first-line chemotherapy. In patients whose cancer responds or who have stable disease, maintenance avelumab can be offered [276]. Depending on the extent of the nodal disease (i.e., cN1/N2) surgical resection with LN dissection can be discussed after initial systemic therapy. In patients whose cancer progress, second-line treatment can be offered, similar to metastatic disease [277, 278].

### 7.3.2 *Distant metastases*

#### 7.3.2.1 *Systemic treatments*

##### 7.3.2.1.1 First-line setting

##### 7.3.2.1.1.1 Patients fit for cisplatin-based combination chemotherapy

Upper tract UC and urothelial BC both respond to systemic platinum-based chemotherapy. 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 [279]. Therefore, cisplatin-containing combination chemotherapy is the standard treatment for advanced or metastatic UTUC [2]. A number of cisplatin-containing chemotherapy regimens have proven efficacy although gemcitabine and cisplatin are the most widely used. The use of cisplatin-based chemotherapy is widely considered in patients with eGFR > 45 mL/min [279].

The efficacy of immunotherapy using PD1 or PD-L1 inhibitors has been evaluated in the first-line setting for the treatment of cisplatin/carboplatin-fit patients with metastatic UC, including those with UTUC [280]. First-line immune checkpoint inhibitors or the combination of platinum-based chemotherapy with immune checkpoint inhibitors have not resulted in positive significant survival advantages and are not currently recommended [281-283].

##### 7.3.2.1.1.2 Patients unfit for cisplatin-based combination chemotherapy

Carboplatin-based chemotherapy is recommended in patients unfit for cisplatin [2]. Carboplatin with gemcitabine is the preferred regimen [284], irrespective of PDL-1 status. In a recent critical re-analysis of RCTs comparing OS after cisplatin vs. carboplatin-based regimens in advanced UC, cisplatin conferred a minor OS benefit compared to carboplatin [285].

##### 7.3.2.1.1.3 Maintenance therapy after first-line platinum-based chemotherapy

Maintenance avelumab is recommended in patients with complete/partial response or stable disease after 4–6 cycles of platinum-based chemotherapy. 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) [276, 286]. 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) [287].

##### 7.3.2.1.1.4 Patients unfit for platinum-based combination chemotherapy

Pembrolizumab or atezolizumab are alternative choices for patients who are PD-L1 positive and not eligible/fit for platinum-based chemotherapy. 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 [288]. 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 [289]. Median OS in the overall cohort was 15.9 months and treatment-related toxicity was in line with previous studies [282].

##### 7.3.2.1.2 Second-line setting

##### 7.3.2.1.2.1 Immunotherapy

A phase III RCT including 542 patients who received prior platinum-based chemotherapy for advanced UC showed that pembrolizumab decreased 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) [290]. 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 relapsed after platinum-based chemotherapy and failed to show a significant OS advantage [291].

Other immunotherapies such as nivolumab [292], avelumab [293, 294] and durvalumab [295] have shown objective response rates ranging from 17.8% [295] to 19.6% [292] 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 [294].

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 [296]. 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 [297].

#### 7.3.2.1.2.2 Novel agents

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

Erdafitinib, a pan-*FGFR* tyrosine kinase inhibitor of *FGFR1–4*, was associated with a 40% radiological response rate (RECIST) in a phase II trial of 99 patients with locally-advanced or metastatic UC who progressed after first-line chemotherapy and harboured a *FGFR* DNA genomic alterations (*FGFR2/3* mutations or *FGFR3* fusions) [298]. This study included 23 UTUC patients with visceral metastases showing a 43% radiological response rate. No OS data are available to date.

##### 7.3.2.1.2.2.2 Antibody drug conjugates (ADC)

A phase II study enrolled 89 patients (of whom 43% had UTUC) with cisplatin-unfit metastatic UC progressing after therapy with PD-1 or PD-L1 inhibitors. All patients received the antibody–drug conjugate enfortumab vedotin. The objective radiological response rate (RECIST) was 52% of which 20% of patients achieved complete response [299]. In a phase III trial of enfortumab vedotin for the treatment of patients with locally-advanced or metastatic UC who had previously received platinum-containing chemotherapy and had disease progression during or after treatment with a PD-1 or PD-L1 inhibitor, enfortumab vedotin significantly prolonged survival as compared with standard chemotherapy (median OS 12.88 vs. 8.97 months) [300].

#### 7.3.2.1.3 Third-line setting

In an open-label phase II trial a total of 108 patients with metastatic UC who progressed after platinum-based chemotherapy and checkpoint inhibitors were treated with the antibody–drug conjugate sacituzumab govitecan. The objective radiological response rate was 27%, with median duration of response of 7.2 months, median PFS of 5.4 months and median OS of 10.9 months. However, the proportion of patients with UC was not mentioned in the publication [301].

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-based chemotherapy and immune checkpoint inhibitors [302]. 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.

#### 7.3.2.2 Surgery

##### 7.3.2.2.1 Radical nephroureterectomy

Data regarding RNU in the metastatic setting are lacking with mainly retrospective observational studies [303–305].

Although evidence remains very limited, RNU may be associated with CSS [304, 306, 307] and OS benefit in selected patients, especially those fit enough to receive cisplatin-based chemotherapy [303, 304]. It is noteworthy that these benefits may be limited to those patients with only one metastatic site [304]. 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 [20, 118] (LE: 3).



### 7.3.2.2.2 Metastasectomy

There is no UTUC-specific study supporting the role of metastasectomy in patients with advanced disease. Reports suggesting that resection of metastatic lesions could be safe and oncologically beneficial in selected patients should be interpreted with caution [308-312]. 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 (LE: 3).

### 7.3.3 Summary of evidence and recommendations for the treatment of metastatic UTUC

Summary of evidence	LE
Cisplatin-based combination chemotherapy can improve median survival.	2
Cisplatin-containing combination chemotherapy is the standard of care in advanced or metastatic patients fit enough to tolerate cisplatin.	1b
Carboplatin-based combination chemotherapy offers a survival benefit in cisplatin unfit patients.	1b
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 either 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 whose disease has 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 unfit for platinum-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 unfit for platinum-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 was associated with radiological response in platinum-refractory patients with locally-advanced or metastatic UC and <i>FGFR</i> DNA genomic alterations ( <i>FGFR2/3</i> mutations or <i>FGFR3</i> fusions).	2a
Enfortumab vedotin was associated with OS benefit in patients who had previously received platinum-containing chemotherapy and experienced disease progression during or after treatment with a PD-1 or PD-L1 inhibitor.	1b
Palliative nephroureterectomy can improve quality of life by controlling symptomatic disease.	3
RNU can confer a survival benefit in highly selected patients.	4

Recommendations	Strength rating
<b>First-line treatment for platinum-eligible patients</b>	
Offer platinum combination chemotherapy to platinum-eligible patients.	Strong
Offer cisplatin-based chemotherapy with gemcitabine/cisplatin or HD-MVAC to cisplatin-eligible patients.	Strong
Offer maintenance avelumab to patients who did not have disease progression after 4 to 6 cycles of gemcitabine plus cisplatin/carboplatin.	Strong
<b>First-line treatment in patients ineligible for cisplatin or carboplatin</b>	
Offer gemcitabine/carboplatin chemotherapy to cisplatin-ineligible patients.	Strong
Offer checkpoint inhibitors pembrolizumab or atezolizumab to patients with PD-L1 positive tumours.	Weak
<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 enfortumab vedotin to patients previously treated with platinum-containing chemotherapy and who had disease progression during or after treatment with a PD-1 or PD-L1 inhibitor.	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
Offer erdafitinib as subsequent-line therapy to platinum-refractory patients with <i>FGFR</i> DNA genomic alterations ( <i>FGFR2/3</i> mutations or <i>FGFR3</i> fusions).	Weak
Offer nephroureterectomy as a palliative treatment to symptomatic patients with resectable locally-advanced tumours.	Weak

*DNA = deoxyribonucleic acid; FGFR = fibroblast growth factor receptors; HD-MVAC = high-dose intensity methotrexate, vinblastine, adriamycin plus cisplatin; PD-L1 = programmed death ligand 1.*

## 8. FOLLOW-UP

The aims for follow-up after treatment for UTUC are to comply with patient rehabilitation needs, to detect recurrent or new primary tumours within the urothelium, and to detect regional and distant metastases. Patient, tumour and treatment characteristics impact, when designing interval, length and modalities for follow-up in the individual patient. Bladder recurrence is not considered a distant recurrence. Unfortunately, the heterogeneity of available studies on disease-recurrence in UTUC is significant, and recommendations on follow-up have a low level of evidence at best.

*After RNU for low-risk tumours*, a negative cystoscopy at three months post-operatively, a subsequent cystoscopy 9 months later and yearly cystoscopies for 5 years based on follow-up data in low-risk Ta BC [313]. Screening for metastases during follow-up is not mandatory, nor is CT urography mandatory in case of a tumour-free bladder due to a low risk of metachronous UTUC [314].

*When RNU has been performed for high-risk tumours*, stringent follow-up is mandatory to detect metachronous bladder tumours (probability increases over time [315]), local recurrence, and distant metastases. The risk of bladder recurrences and other-site recurrences decreases 4 years after RNU, suggesting that less vigorous annual cystoscopies and cross-sectional imaging including CT urographies thereafter may apply [316].

*After kidney-sparing management for low-risk UTUC*, and no upstaging or upgrading occurred after the early second-look ureteroscopy after 6-8 weeks [204] or in the resection specimen after segmental ureteric resection, cystoscopy and CT-urography at 3 and 6 months, and then yearly for 5 years. The risk for bladder recurrences beyond 5 years is limited (6%) [317].

*In patients treated with kidney-sparing for high-risk tumours*, the indication (imperative vs. non-imperative) affects the surveillance regimen by the consequences of recurrent disease. Still, the ipsilateral UUT requires careful and long-term follow-up due to the high risk of disease recurrence [203, 318, 319] and progression following RNU, even beyond 5 years [320].

Surveillance regimens are based on cystoscopy and urinary cytology [15, 315]. There are, however, several unanswered questions related to the optimal follow-up of patients treated for both low-risk and high-risk UTUC, of which some are:

- The added value of new urinary markers compared to cytology in voided urine samples [321].
- The effect of the Paris System on sensitivity and specificity of voided and selective urinary cytology during follow-up of UTUC, especially in high-risk tumours [322].
- If adjuvant upper tract instillations have been administered after endourologic kidney-sparing management, will that allow for less vigorous follow-up?
- The role of ureteroscopies of the ipsilateral upper urinary tract during follow-up after endourologic kidney-sparing treatment vs. CT urography and voided urinary cytology.

Additionally, it is not known how patients with Lynch syndrome, without and with UTUC, should be followed long-term given the inadequacy of surveillance based on urinalysis for nonvisible haematuria [323] and urine cytology [324], particularly in those individuals who are *MSH2* mutation carriers [31] and those who already have developed a UTUC. Section 8.1 presents the summary of evidence and recommendations for follow-up of UTUC.

## 8.1 Summary of evidence and recommendations 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 if no second-look ureteroscopy was performed.	Weak
<i>High-risk tumours</i>	
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/>.

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## 11. CITATION INFORMATION

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