# EAU Guidelines on

# Upper Urinary Tract Urothelial Carcinoma

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# 1. INTRODUCTION

## 1.1 Aim and scope

This overview represents the updated European Association of Urology (EAU) Guidelines for the management of upper urinary tract urothelial carcinoma (UTUC). Separate EAU Guidelines are available addressing non-muscle-invasive bladder cancer (NMIBC) [1], muscle-invasive and metastatic bladder cancer (MIBC) [2], and primary urethral carcinoma (PUC) [3].

It must be emphasised that clinical Guidelines present the best evidence available to the experts, but following guidelines 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 - including 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 EAU Guidelines Panel on UTUC consists of an international multidisciplinary group of clinicians, including urologists, uro-oncologists, a pathologist and patient representatives. Members of this Panel have been selected based on their expertise and to represent the professionals treating patients suspected of harbouring urothelial carcinoma (UC). Everyone involved in the production of this document have submitted potential conflict of interest statements, which can be viewed on the EAU website: https://uroweb.org/guidelines/upper-urinary-tract-urothelial-cell-carcinoma/panel/.

## 1.3 Available publications

A quick reference document (Pocket Guidelines) is available online and in print, presenting the main findings of the UTUC Guidelines. This reference document is an abridged version that may require consultation together with the full text version. Several scientific publications are available; the most recent scientific summary was published in 2025 [4]. All documents are accessible on the EAU website: https://uroweb.org/guideline/upper-urinary-tract-urothelial-cell-carcinoma/. An EAU Guidelines App for iOS and Android devices is also available containing the Pocket Guidelines, interactive algorithms and calculators, clinical decision support tools, guidelines cheat sheets, and links to the full text guidelines.

## 1.4 Publication history and summary of changes

The first EAU Guidelines on UTUC were published in 2011. Standard procedure for EAU Guidelines includes an annual assessment of newly published literature in the field to guide future updates. The 2026 UTUC Guidelines presents a limited update of the 2025 version.

### *1.4.1 Summary of changes*

For the 2026 UTUC Guidelines, new and relevant evidence was identified, collated and appraised through a structured assessment of the literature for all sections of the Guidelines. Key changes include:

- In Section 3.4, the prognostic value of fibroblast growth factor receptor *(FGFR)* 3 expression in UTUC is discussed.
- In Chapter 4, the 9$^{th}$ edition (2025) of the Tumour, Node, Metastasis (TNM) classification is incorporated.
- In Section 5.4, the evidence base related to cytology and urinary biomarkers is developed to provide greater clarity.
- In Section 7.1.2, the lack of data related to both renal preservation after endoscopic treatment and ablation performed with lasers is discussed.
- In Section 7.2.1.a.2, techniques related to bladder cuff management are elaborated upon.
- In Section 7.2.1.a.3, the patient criteria for lymph node dissection (LND) are discussed.
- In Section 7.2.1.b.1, two retrospective studies related to distal ureterectomy are added.
- In Section 7.2.2.a.3, a study related to chemoimmunotherapy is included.
- In Section 7.2.2.b.2, a study related to the use of adjuvant bladder instillations in a preoperative setting is included.
- In Section 7.3.1, the options related to the treatment of patients with clinical locoregional lymph node (LN) metastases, and the evidence in this regard, are discussed.
- In Chapter 8, the recommendations for the follow-up of UTUC in patients with high-risk tumours after kidney-sparing management are updated.

# 2. METHODS

## 2.1 Data identification

For the 2026 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 1 May 2024 and 1 May 2025. 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 417 unique records were identified, retrieved and screened for relevance. A detailed search strategy is available on the EAU website: https://uroweb.org/guidelines/upper-urinary-tract-urothelial-cell-carcinoma/publications-appendices.

Recommendations within the Guidelines are developed by the Panels to prioritise clinically important care decisions. 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 the nature and variability of patient values and preferences. This decision process, which can be reviewed in the strength rating forms that accompany each guideline recommendation, addresses a number of key elements:

1. the overall quality of the evidence that 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 and certainty of patient values and preferences on the intervention.

Strong recommendations typically indicate a high degree of evidence quality and/or a favourable balance of benefit to harm and patient preference. Weak recommendations typically indicate availability of lower quality evidence and/or equivocal balance between benefit and harm, and uncertainty or variability of patient preference [6].

Additional methodology information and a list of associations endorsing the EAU Guidelines can be found on the EAU website: https://uroweb.org/eau-guidelines/methodology-policies.

## 2.2 Review

The UTUC Guidelines were subject to peer-review prior to publication in 2023.

# 3. EPIDEMIOLOGY, AETIOLOGY AND PATHOLOGY

## 3.1 Epidemiology

Urothelial carcinoma is the second most common urological malignancy in developed countries [7]. It can be localised in the lower (bladder and urethra) and/or the upper (pyelocaliceal cavities and ureter) urinary tract. Bladder cancer (BC) accounts for 90-95% of UCs, whilst UTUC accounts for only 5-10% of UCs with an estimated annual incidence in Western countries of nearly two cases per 100,000 inhabitants [1]. This rate has risen in the past few decades, likely as a result of improved detection and the aging population [8, 9].

The peak incidence is in individuals aged 70-90 years, and UTUC is twice as common in males [10]. A retrospective international registry including data from 2,380 patients diagnosed between 2014 and 2019 (101 centres from 29 countries) confirmed that UTUC patients were predominantly male (70.5%) and 53.3% were former or current smokers. The majority of patients (53%) were diagnosed after they presented with symptoms, mainly visible haematuria [11]. A meta-analysis pooling 44 studies showed a pooled UTUC incidence rate of 0.75% in patients with visible haematuria and 0.17% for those with non-visible haematuria [12]. In addition, approximately two-thirds of patients who present with UTUCs have muscle-invasive disease at diagnosis compared to 15-25% of patients diagnosed with *de novo* BC [13]. The higher incidence of muscle-invasive disease in UTUC versus BC has been confirmed in population-based studies from Germany and England, suggesting that muscle-invasive UTUC represents approximately half of incident cases [14, 15]. Approximately 9% of patients present with metastases [8, 16-18].

Pyelocaliceal tumours are approximately twice as common as ureteral tumours, and multifocal tumours are found in approximately 10-20% of cases [19]. The presence of concomitant carcinoma *in situ* (CIS) of the upper tract is between 11% and 36% [20], with an increased incidence of higher tumour stage and ureteral tumour location found in a population-based series [8, 21].

Concurrent BC is present in 17% of UTUC cases [22], whilst a prior history of BC is found in 41% of American males but in only 4% of Chinese patients [23]. In high-risk NMIBC patients treated with intravesical bacillus Calmette-Guérin (BCG), the prevalence of UTUC ranged from 7.5% to 25% [24-26] and from 3% to 5% in those with MIBC treated with radical cystectomy (RC) [27, 28]. Concomitant BC when diagnosed with UTUC is associated with more advanced disease, both in the upper tract and bladder [29], and corresponds to worse cancer-specific survival (CSS) [30, 31]. Metachronous BC on the other hand, does not seem to have an impact on CSS [31].

Following treatment for UTUC, recurrence in the bladder occurs in approximately 30% of UTUC patients, depending on patient-, tumour- and treatment-specific characteristics [32], compared to a 2-5% recurrence rate in the contralateral upper tract [33].

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 [34].

## 3.2 Risk factors

### *3.2.1* ***Environmental risk factors***

A number of environmental risk factors have been implicated in the development of UTUC [19, 35]. With the exception of smoking and aristolochic acid, no strong evidence supports the causative role for these factors. Tobacco exposure increases the relative risk of developing UTUC by 2.5 to 7.0 times [36-38].

Aristolochic acid, a nitrophenanthrene carboxylic acid produced by aristolochia plants, exerts negative effects on the urinary system by irreversibly injuring renal proximal tubules, resulting in chronic tubulointerstitial disease, while the mutagenic properties of this carcinogen can lead to UTUC [39-41]. However, it is estimated that fewer than 10% of individuals exposed to aristolochic acid develop UTUC [41]. Aristolochic acid has also been linked to BC, renal cell carcinoma, hepatocellular carcinoma and intrahepatic cholangiocarcinoma [42]. Following bioactivation, aristolochic acid reacts with genomic deoxyribonucleic acid (DNA) to form aristolactam-deoxyadenosine adducts [43]. These lesions persist for decades in target tissues, serving as robust biomarkers of exposure [44]. These adducts generate a unique mutational spectrum, characterised by A > T transversions located predominately on the non-transcribed strand of DNA [42, 45]. Two routes of exposure to aristolochic acid are known: (i) environmental contamination of agricultural products by aristolochia plants, as reported for Balkan endemic nephropathy [46]; and (ii) ingestion of aristolochia-based herbal remedies [47, 48]. Aristolochic acid-associated UTUC is more common in females [49, 50], but females with aristolochic acid UTUC have a better prognosis than their male counterparts.

Other environmental risk factors may include the presence of arsenic in drinking water, which has been tentatively linked to UTUC, especially in Taiwan and Chile [51, 52]. Arsenic mitigation from drinking water in Taiwan has also been shown to reduce the incidence of UTUC in a large population-based study [53]. Consumption of arsenic in drinking water and aristolochia-based herbal remedies together appears to have an additive carcinogenic effect [54].

In addition, alcohol consumption may be associated with the development of UTUC. A large case-control study (1,569 cases and 506,797 controls) has shown a significantly higher risk of UTUC in drinkers compared to never drinkers (odds ratio [OR]: 1.23; 95% confidence interval [CI]: 1.08-1.40). Compared to never drinkers, the risk threshold for UTUC was > 15g of alcohol/day. A dose-response has been observed [55].

### *3.2.2* ***Genetic risk factors***

Lynch syndrome is characterised by a predisposition to early onset colorectal cancer and several extra-colonic malignancies related to pathogenic germline mutations in one allele of the mismatch repair *(MMR)* genes *MSH2*, *MSH6*, *MLH1* or *PMS2*. After colorectal and endometrial cancers, UTUC is the third most common malignancy in the Lynch syndrome spectrum [56]. Identifying Lynch syndrome's related UTUC has important clinical implications for both the patient and their relatives given the high risk of developing subsequent multiple different malignancies in the carrier and the strong hereditary predisposition of this condition. Germline mutations in MMR genes are found in up to 9% of patients with UTUC compared to 1% of patients with BC [57].

From a genetic perspective, the majority of tumours develop in *MSH2* and *MSH6* mutation carriers [58]. The carcinogenesis is related to the somatic mutation of the second allele of the germline-mutated MMR gene. This will result in a deficient MMR (dMMR) system related to the loss of the expression of the corresponding protein MSH2, MSH6, MLH1 or PMS2 in immunochemistry, which can be responsible for a microsatellite instability identified using the polymerase chain reaction (PCR) method.

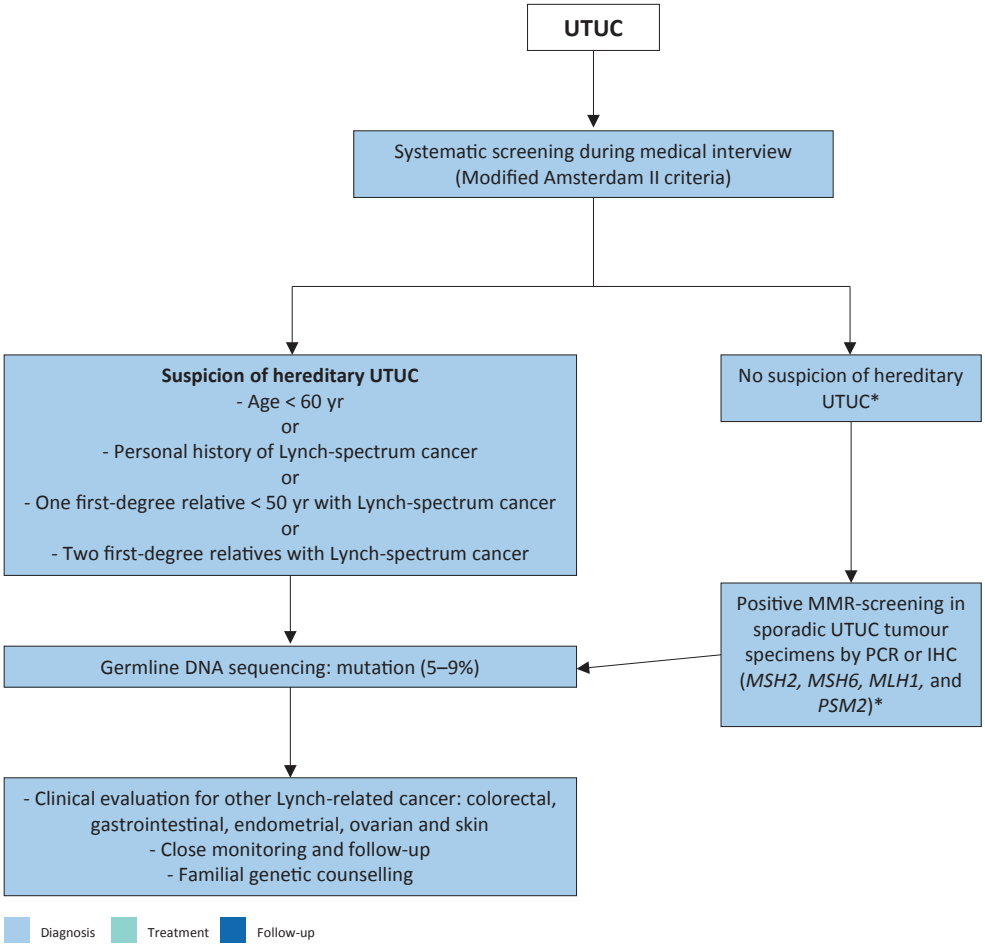
From a clinical perspective, although the PREMM5 model has been developed to estimate the cumulative probability of an individual carrying a germline mutation related to Lynch syndrome [59], the Amsterdam II criteria remains predominantly used to identify families that are at increased risk of Lynch syndrome [60]. The latter includes:

- at least three relatives with a Lynch-associated cancer (colorectal, endometrium, small bowel or UTUC);
- a first degree relative to the other two;
- at least two successive affected generations;
- at least one relative diagnosed before the age 50;
- exclusion of familial adenomatous polyposis in the colorectal cancer cases; and
- pathological confirmation of the diagnosis.

A study of 115 consecutive UTUC patients reported that 13.9% screened positive for potential Lynch syndrome using the Amsterdam II criteria and 5.2% had confirmed Lynch syndrome [61].

Another UTUC-specific study has suggested that an age < 60 at initial diagnosis and a personal history of any other Lynch-related malignancy could both be associated with an increased risk of Lynch syndrome in these patients [62]. A simplified screening tool for UTUC patients has been proposed that incorporates the aforementioned two factors together with two additional criteria derived from the Amsterdam II criteria, being one first-degree relative with a Lynch-related cancer diagnosed before the age of 50, and two first-degree relatives with Lynch-related cancer regardless of age [63]. Using this simplified screening tool, the proportion of UTUC patients with a suspicion of Lynch-related disease could be more than 20% [63]. Importantly, patients with UTUC who are identified as being at high risk for Lynch syndrome based on clinical criteria should undergo germline DNA sequencing and family counselling [64, 65] (Figure 3.1). Nonetheless, given the limited diagnostic performance of clinical criteria, UTUC patients without suspicion for genetic predisposing factors could be tested for microsatellite instability (MSI) or dMMR using PCR or immunochemistry on tumour specimens, respectively [57, 66-70].

**Figure 3.1: Selection of patients with upper urinary tract urothelial carcinoma for Lynch syndrome screening during the first medical interview**




**These patients may benefit from MMR deficiency screening using PCR or IHC. A positive result should prompt subsequent testing for germline DNA sequencing mutations.*
*DNA = deoxyribonucleic acid; IHC = immunohistochemistry; MMR = mismatch repair; Mismatch repair genes = MSH2, MSH6, MLH1 and PMS2; PCR = polymerase chain reaction; UTUC = upper urinary tract urothelial carcinoma.*

Differences in exposure and susceptibility to carcinogens such as smoking may explain why patients with similar predisposing genetic mutations vary in their progression to overt disease. Some genetic polymorphisms are associated with an increased risk of cancer or more rapid disease progression that introduces variability in the inter-individual susceptibility to the risk factors mentioned previously. So far, two UTUC-specific polymorphisms have been reported [71]. Upper urinary tract UCs may also share some molecular pathways with BC [34]. However, in a large population-based case control study, familial clustering independent of smoking-related behaviours was only observed in BC patients, not in UTUC patients [72].

#### *3.2.3 History of bladder cancer*

A history of BC is associated with a higher risk of developing UTUC (see section 3.1). Patients requiring ureteral stenting at the time of transurethral resection of the bladder, including prior to RC, have been shown to have a higher risk for upper tract recurrence [73, 74].

## 3.3 Histology and classification

#### *3.3.1 Histological types*

Upper urinary tract tumours are almost always UCs, with pure non-urothelial histology being rare [75, 76]. However, histological subtypes or divergent differentiation are present in approximately 14% of UTUCs treated with radical nephroureterectomy (RNU) [77]. Pure squamous cell carcinoma of the urinary tract is often assumed to be associated with chronic inflammatory diseases and infections arising from urolithiasis [78, 79]. Urothelial carcinoma with divergent squamous differentiation (i.e. squamous subtype) is the most prevalent subtype. Squamous subtype was observed in 63% of all individuals with histological subtypes or divergent

differentiation, and this subtype presents in approximately 13% of high-grade cases [77, 78]. Upper urinary tract UCs with different subtypes are high-grade and have a worse prognosis compared to pure UC [80-82]. Other subtypes are rare; inverted growths can be observed and can be difficult for staging [82-84].

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 [85].

### 3.4 Molecular background of upper urinary tract urothelial carcinoma

A number of studies focussing on molecular classification have been able to demonstrate genetically distinct groups of UTUC by evaluating DNA, ribonucleic acid (RNA) and protein expression. The most common genomic alterations included *FGFR* 3, chromatin remodelling genes (i.e. *KMT2D* and *KDM6A*), *TP53/MDM2* and other typical tumour suppressors/oncogenes, such as *CDKN2A* or *RAS* [86-89].

It has also been shown that UTUC has a T-cell depleted immune contexture and activated *FGFR* 3 signalling [90]. Different mutational molecular variants with different gene expression, tumour location and outcome have been identified [89, 91]. Currently, testing for *FGFR* 3 alterations in the metastatic setting is the only relevant molecular background predicting response to erdafitinib treatment. Evidence suggests that *FGFR* 3 expression in UTUC provides prognostic value. High *FGFR* 3 expression is linked to an immune cold phenotype and may be linked to favourable prognosis and differential response to immunotherapy [90, 92].

### 3.5 Summary of evidence and recommendations for epidemiology, aetiology and histology

| 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 to screen patients for Lynch syndrome using modified Amsterdam II criteria. | Strong |
| Perform germline deoxyribonucleic acid sequencing in patients with clinical suspicion of hereditary upper urinary tract urothelial carcinomas (UTUC). | Strong |
| Offer testing for mismatch repair proteins or microsatellite instability in patients without clinical suspicion of hereditary UTUC. | Weak |

# 4. STAGING AND CLASSIFICATION SYSTEMS

### 4.1 Classification

The classification and morphology of UTUC and BC are similar [1]. However, because of the difficulty in adequate sample acquisition, it is often difficult to distinguish between non-invasive papillary tumours [93], flat lesions (CIS), and invasive carcinoma in biopsies. Therefore, histological grade is often used for clinical decision-making as it is strongly associated with pathological stage [94].

### 4.2 Tumour, Node, Metastasis classification

Table 1 shows the TNM classification [95]. The regional 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 2022, the World Health Organization (WHO) published a new histological classification of UCs that provides a different patient stratification between individual categories compared to the older 1973 WHO classification [96-98]. These Guidelines are still based on both the 1973 and 2004/2016 WHO classifications since most published data use the 1973 classification [93].

**Table 1: Tumour, Node, Metastasis classification 2025 for upper tract urothelial cell carcinoma** [95]

| | |
|---|---|
| **T - Primary tumour** | |
| TX | Primary tumour cannot be assessed |
| T0 | No evidence of primary tumour |
| Ta | Non-invasive papillary carcinoma |
| Tis | Carcinoma *in situ* |
| T1 | Tumour invades subepithelial connective tissue |
| T2 | Tumour invades muscularis |
| T3 | (Renal pelvis) Tumour invades beyond muscularis into peripelvic fat, or renal parenchyma (Ureter) Tumour invades beyond muscularis into periureteric fat |
| T4 | Tumour invades adjacent organs or through the kidney into perinephric fat |
| **N - Regional lymph nodes** | |
| NX | Regional lymph nodes cannot be assessed |
| N0 | No regional lymph node metastasis |
| N1 | Metastasis in a single lymph node 2 cm or less in the greatest dimension |
| N2 | Metastasis in a single lymph node more than 2 cm, or multiple lymph nodes |
| **M - Distant metastasis** | |
| M0 | No distant metastasis |
| M1 | Distant metastasis |

# 5. DIAGNOSIS

## 5.1 Symptoms

The diagnosis of UTUC may be incidental or symptom related. The most common symptom is haematuria [11]. Flank pain due to clot or tumour tissue obstruction can occur in 20-32% of cases [11]. Preoperative symptoms at diagnosis are associated with a worse prognosis [99]. Systemic symptoms (including anorexia, weight loss, malaise, fatigue, fever, night sweats and cough) in patients with UTUC should prompt evaluation for metastases associated with a worse prognosis [11].

## 5.2 Imaging

### *5.2.1 **Computed tomography***

Computed tomography (CT) urography has the highest diagnostic accuracy of the available imaging techniques [100]. 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) [101].

Rapid acquisition of thin sections allows high-resolution isotropic images of both upper urinary tracts 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 on CT is highly predictive of metastases in UTUC [102, 103]. The risk of thoracic metastases is extremely low in low-risk UTUC (see Chapter 6 for UTUC risk classification variables).

### *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 [104]. The sensitivity of MR urography is 75% after contrast injection for tumours < 2cm [104]. For the diagnosis and staging of UTUC, CT urography is more sensitive and specific compared to MR urography [105].

#### 5.2.3 *$^{18}$F-Fluorodeoxglucose positron emission tomography/computed tomography*

A retrospective multicentre publication on the use of $^{18}$F-Fluorodeoxglucose positron emission tomography/CT (FDG-PET/CT) for the detection of nodal metastasis in 117 surgically treated UTUC patients reported promising sensitivity and specificity of 82% and 84%, respectively. Suspicious LNs on FDG-PET/CT were associated with worse recurrence-free survival (RFS) [106]. These results warrant further validation and comparison with MR and CT. Assessment of (nodal and distant) metastases in patients unfit for iodinated contrast media due to renal impairment and/or allergy can also be performed using FDG-PET/CT.

### 5.3 Cystoscopy

Urethrocystoscopy is an integral part of the UTUC work-up to rule out concomitant BC [8, 22].

### 5.4 Cytology and urinary markers

Voided cytology may indicate high-grade UTUC when cystoscopy is normal, and in the absence of CIS in the bladder and prostatic urethra [1, 107]. However, voided urinary cytology is less sensitive for detecting UTUC compared to selectively obtained cytology from the affected upper tract [108]. Data indicate that barbotage cytology can detect up to 91% of tumours [109]. Barbotage cytology obtained from the renal cavities and ureter is preferred prior to the use of contrast agents for retrograde ureteropyelography as it may compromise cytological specimen quality [107, 109]. Retrograde ureteropyelography remains an option to detect UTUC [94, 110, 111].

Liquid-based biomarkers have the potential to be an adjunct to existing diagnostic modalities in the evaluation of suspected UTUC by improving diagnostic pathways, risk stratification and reducing invasive surveillance strategies. A variety of urinary biomarkers adopting varying technologies have been described for UTUC, such as DNA methylation panels, RNA-based signature panels, fluorescence *in situ* hybridisation (FISH), protein markers panels (NMP-22, BTA, BTA-stat, uCyt+, surviving, p16/Ki-67), and genetic mutation panels for both bladder-based and upper tract urine. Preliminary data suggest that RNA-based signature panels and DNA methylation panels have favourable diagnostic performance for bladder-based urine [112-114].

For upper tract urine, the reported diagnostic performance for Epicheck® (DNA methylation) and UroVysion® (FISH) offer a reasonable balance between sensitivity and specificity. The reported sensitivities of Epicheck® range from 65% to 83%, while specificity ranges from 79% to 81% [115-117]. The reported sensitivities of UroVysion® range from 78% to 93% and specificities from 51% to 91% [116, 118-120]. Both panels have high sensitivity for high-grade disease [116, 120, 121].

Preliminary data would suggest circulating tumour DNA (ctDNA) incorporating plasma copy number burden > 6.5 is a promising blood-based biomarker in predicting advanced invasive disease. One study reported a sensitivity of 79% (95% CI: 49-95%) and specificity of 94% (95% CI: 79-100%) for predicting ≥ pT2 and high-grade disease [122].

### 5.5 Diagnostic ureteroscopy

Diagnostic ureteroscopy (URS) may be used to confirm the diagnosis of UTUC. Complete inspection of the affected upper tract allows for detailed tumour mapping, assessment of tumour size and multifocality, as well as a targeted biopsy of suspicious lesions, before considering kidney-sparing options. Ureteroscopic biopsies can determine tumour grade in over 90% of cases, with a low false-negative rate regardless of sample size [123]. However, undergrading and understaging leading to inaccurate risk stratification occurs with ureteroscopic diagnostic biopsy compared to nephroureterectomy specimens [94, 124, 125].

Ureteroscopy also enables selective ureteral sampling for cytology [111, 126, 127]. However, stage assessment based on ureteroscopic biopsy may be inaccurate, as small biopsy specimens frequently lack lamina propria. Integrating the results of ureteroscopic biopsy grading, imaging findings and urinary cytology can improve risk stratification and inform the decision-making process between RNU and kidney-sparing options [127, 128]. A meta-analysis comparing patients who underwent URS prior to RNU with those who did not, found that eight out of 12 studies reported an increased risk of intravesical recurrence associated with URS [129]. Performing a biopsy during URS was also identified as a risk factor for intravesical recurrence [129]. A second systematic review of 16 studies demonstrated that URS alone was not significantly associated with intravesical recurrence. However, URS with a concomitant biopsy significantly increased the risk for subsequent intravesical recurrence without an impact on extra urinary tract recurrences and overall survival (OS) [130].

Technical developments in flexible ureteroscopes and the use of novel imaging techniques may improve visualisation and diagnosis of flat lesions [131]. Narrow-band imaging is a promising technique, but results are preliminary [132]. 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 [133, 134].

### 5.6 Molecular testing

Alterations in *FGFR* 2/3 should be tested for by means of next generation sequencing (see section 7.3.2.b.3) in the metastatic setting, preferably from an invasive part of the tumour or metastatic site [135, 136].

### 5.7 Summary of evidence and recommendations for the diagnosis of upper urinary tract urothelial carcinoma

| Summary of evidence | LE |
|---|---|
| The diagnosis and staging of UTUC is best achieved with CT urography and URS. | 2a |
| Selective urinary cytology has high sensitivity in high-grade tumours, including CIS. | 3 |
| Urethrocystoscopy can detect concomitant BC. | 2a |

| Recommendations | Strength rating |
|---|---|
| Perform a urethrocystoscopy to rule out bladder tumour. | Strong |
| Perform voided urinary cytology in any case of suspicion of upper tract tumour. | Weak |
| Perform computed tomography (CT), or magnetic resonance imaging if CT is contraindicated, with urography for diagnosis and staging of all upper tract tumours. | Strong |
| Perform a chest CT in high-risk tumours (see Figure 6.1). | Strong |
| $^{18}$F-Fluorodeoxglucose positron emission tomography/CT may be used to rule out metastases in high-risk disease. | Strong |
| Use diagnostic ureteroscopy if imaging and voided urine cytology are not sufficient for the diagnosis and/or risk-stratification of patients suspected to have upper urinary tract urothelial carcinomas. | Strong |
| Test for fibroblast growth factor receptor 2/3 alterations at initial diagnosis in the metastatic setting. | Strong |

# 6. RISK STRATIFICATION

### 6.1 Factors for clinical decision-making

The main prognostic factor in UTUC is pathological tumour stage [127, 137-139]. Upper urinary tract UCs that invade the muscle have a poor prognosis. In a large Dutch series of UTUC, five-year CSS was 86% for non-muscle-invasive tumours, 70% for muscle-invasive organ-confined tumours and 44% for locally advanced tumours [18]. A contemporary Surveillance, Epidemiology, and End Results Program (SEER) analysis of RNUs for high-risk disease showed that five-year CSS was 86% for T1N0, 77% for T2N0, 63% for T3N0, and 39% for T4N0/T any N1-2, respectively [140].

#### *6.1.1 **Pathological grade***

Tumour grading reflects tumour aggressiveness and could serve as a surrogate predictor of disease progression. A higher tumour grade has been associated with high rates of disease recurrence and worse CSS following initial RNU [13, 141]. In fact, histological grade is one of the most important surrogate markers for pathological staging in UTUC. Multiple studies have established a strong correlation between high-grade tumours and advanced pathological stages, particularly muscle-invasive disease (≥ pT2). Similarly, another study found that tumour grade is a reliable predictor of non-organ-confined disease, showing that high-grade tumours have a significantly higher likelihood of metastasis and is an independent predictor of CSS and RFS following RNU [13]. Consequently, histological grade serves as a critical factor in guiding clinical decisions, particularly when imaging and biopsy results are insufficient for accurate staging.

### *6.1.2 **Histological subtypes***

Histological subtypes are associated with worse CSS and OS [80]. The most-studied subtypes are micropapillary [81], squamous differentiation [142] and sarcomatoid [81], all of which are consistently associated with locally advanced disease and worse outcomes [77]. Patients harbouring histological subtypes should be recommended to undergo RNU after a shared decision-making process due to the higher risk of disease progression.

### *6.1.3 **Local invasion on computed tomography***

Computed tomography urography remains the main tool for the initial diagnosis of UTUC. Several studies demonstrate that CT urography provides high diagnostic accuracy for detecting UTUC [101]. A meta-analysis reported that CT urography has a sensitivity of 92% and a specificity of 95% for identifying muscle-invasive disease [101]. Moreover, another study demonstrated that CT can accurately predict pathological stage, particularly when identifying peripelvic fat invasion and non-organ-confined tumours, which are critical indicators of advanced UTUC [143]. While biopsies may sometimes understage UTUC due to limited sample size, CT imaging offers a non-invasive and comprehensive assessment of tumour invasion, particularly in cases of large or deeply invasive lesions [143]. For local staging, CT urography can also provide additional information on local invasion into renal parenchyma, renal pelvis and periureteric tissue [144]. After adjusting for tumour size and hydronephrosis, local invasion on CT remains a significant risk factor for non-organ-confined disease [144]. These findings indicate that CT urography is a valuable modality in the preoperative assessment of UTUC, guiding appropriate treatment strategies based on tumour stage, particularly non-organ-confined tumours. However, its ability to differentiate Ta from T1 from T2 tumours remains low.

### *6.1.4 **Multifocality***

Approximately 7-42% of UTUC patients have been reported to have multifocal tumours [145-149]. Patients with multifocal tumours are more likely to harbour advanced tumour stage and a worse prognosis despite treatment with RNU [145-149]. However, multifocal tumours can also be present in the setting of otherwise low-grade UTUC. It is important to note that the definition of multifocality varies among studies. Some studies consider the number of lesions [148] while others focus on tumour location (i.e. both renal pelvis and ureter) [145-147, 149, 150]. Therefore, tumour multifocality alone should not be used for risk stratification.

### *6.1.5 **Hydroureteronephrosis***

Hydroureteronephrosis has been linked to advanced disease and poor prognosis in patients treated with RNU [102, 151, 152]. A meta-analysis of 22 studies involving 7,542 patients found preoperative hydroureteronephrosis to be significantly associated with ureteral tumour location, advanced tumour stage, and lymph node metastasis [153]. In addition, preoperative hydroureteronephrosis was independently associated with worse OS, CSS and disease-free survival (DFS) [153].

As for multifocality, it is important to note that the definition of hydronephrosis varies among studies with heterogeneity and potential confounding factors. Taking into consideration that some otherwise low-risk tumours might exhibit some degree of upper tract dilation, presence of signs of obstruction should be considered alongside other high-risk factors (see Figure 6.1).

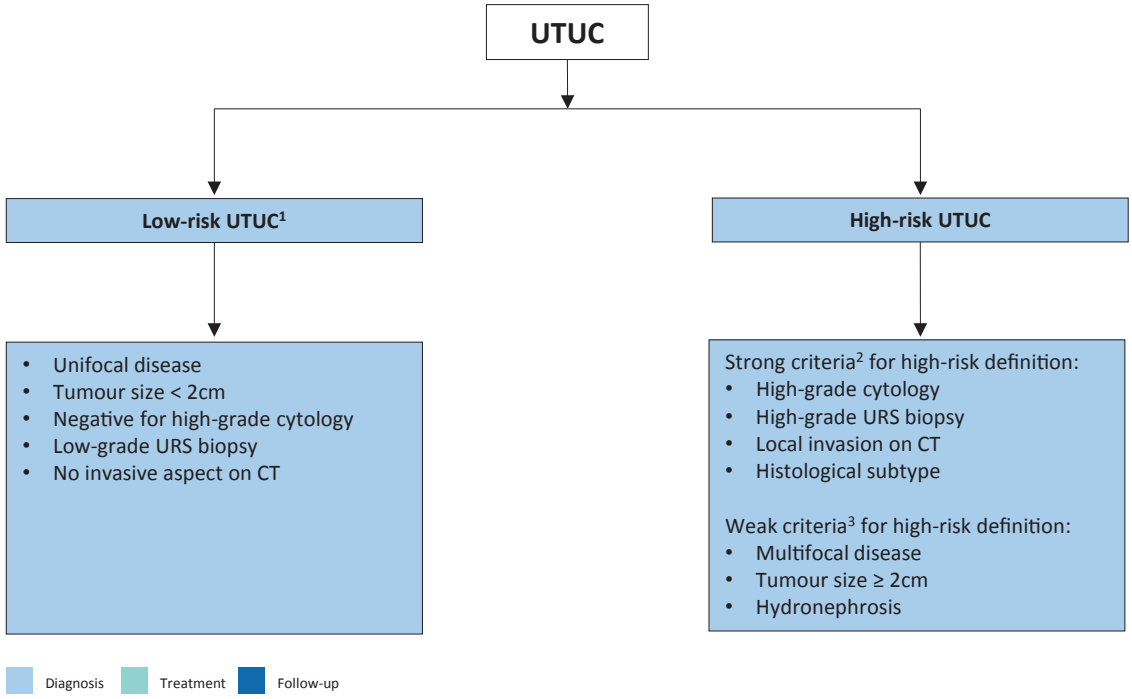
### *6.1.6 **Tumour size***

Increasing tumour size is linked to a higher risk of muscle-invasive and non-organ-confined disease in both ureteral and renal pelvis UTUC cases [154]. A meta-analysis of 32,292 patients confirmed that larger tumours are significantly associated with worse OS, CSS and DFS, as well as intravesical recurrence [154]. In renal pelvis UTUC, where the median tumour size ranges from 3.5 to 4.0cm, each 1cm increase in tumour size elevates the risk of harbouring muscle-invasive disease at RNU by 1.25 times [155]. A multi-institutional study with 932 patients suggested that a 2cm tumour size serves as the optimal threshold for identifying high-risk patients (> pT2 UTUC) [156]. However, measuring tumour size lacks standardisation, leading to inter-assessor variability. Overall, like tumour multifocality and hydroureteronephrosis, tumour size assessment suffers from heterogeneity and potential confounding factors. Tumour size should be considered a continuous variable associated with stage but is insufficient by itself for precise risk stratification.

### *6.1.7 **Risk stratification for clinical decision-making***

Figure 6.1 presents the factors to consider for risk stratification as well as the weight given to each factor. Grade remains the most important surrogate factor reflecting tumour stage and aggressiveness. The level of evidence to individually consider tumour size, multifocality and hydronephrosis as a surrogate for high-risk of progression remains low. Therefore, in the presence of low-grade disease associated with these factors, a shared decision-making process with the patient is important to agree on the therapeutic strategy (kidney-sparing strategy or RNU).

**Figure 6.1: Risk stratification of non-metastatic upper urinary tract urothelial carcinoma according to the risk of progression to a > pT2/non-organ-confined disease**




*1: All these factors must be present.*
*2: Any of these factors must be present.*
*3: In the presence of low-grade tumour, these factors are not strong predictors of invasive disease.*
*CT = computed tomography; URS = ureteroscopy; UTUC = upper urinary tract urothelial carcinoma.*

## 6.2 Bladder recurrence

A meta-analysis of available data has identified significant predictors of bladder recurrence after RNU [32]. Three categories of predictors for increased risk of bladder recurrence were proposed:

- Patient-specific factors, such as male sex, previous BC, smoking and preoperative chronic kidney disease.
- Tumour-specific factors, such as positive preoperative urinary cytology, tumour grade, ureteral location, multifocality, tumour diameter, invasive pT stage and necrosis [157, 158].
- Treatment-specific factors, such as laparoscopic approach, extravesical bladder cuff removal and positive surgical margins.

In addition, the use of invasive diagnostic modalities, particularly URS with biopsy, have been associated with a higher risk of developing bladder recurrence after RNU [159-161].

## 6.3 Summary of evidence and recommendation for the prognosis of upper urinary tract urothelial carcinoma

| Summary of evidence | LE |
|---|---|
| Important prognostic factors for risk stratification include stage, grade, different histological subtypes, tumour size, multifocality and hydronephrosis. | 3 |
| Models are available to predict pT2/non-organ-confined disease and prognosis after RNU. | 3 |
| Patient, tumour and treatment-related factors impact risk of bladder recurrence after both kidney-sparing management and RNU. | 3 |
| Currently, no molecular biomarkers are validated for clinical use. | 3 |

| Recommendation | Strength rating |
|---|---|
| Use prognostic factors to risk-stratify patients for therapeutic guidance. | Strong |

# 7. DISEASE MANAGEMENT

All patients with suspicion of UTUC based on radiology, cystoscopy and urine cytology should be discussed in a multidisciplinary team prior to diagnostic ureteroscopy and the initiation of treatment [162]. This is supported by population-based data reporting increased use of invasive diagnostic modalities in hospitals with a lower caseload [161].

## 7.1 Low-risk disease

### *7.1.1 General considerations on kidney-sparing surgery*

Kidney-sparing surgery for low-risk UTUC reduces the morbidity associated with RNU (e.g. loss of kidney function) without compromising oncological outcomes [163]. In low-risk cancers, kidney-sparing surgery is the preferred approach, because survival is similar to that after RNU [163, 164]. This option should therefore be discussed with all patients with low-risk UTUC, irrespective of the status of the contralateral kidney, as part of a shared decision-making process. Recommendations for kidney-sparing management of UTUC are listed in section 7.1.7.

### *7.1.2 Endoscopic ablation with ureteroscopy*

Endoscopic tumour ablation should be considered in patients with low-risk UTUC [165, 166]. Patients should be informed of the need and be willing and able to comply with an early second-look URS [167] and stringent surveillance, because one in two patients develop ipsilateral upper tract recurrence within two years [168]. Additionally, complete tumour resection or destruction is necessary [167]. Nevertheless, a risk of disease downstaging or progression remains with endoscopic management due to the suboptimal performance of imaging and biopsy for risk stratification and tumour biology [169]. A systematic review confirmed the comparable survival outcomes of endoscopic treatment to those of RNU, but at the cost of higher local recurrence rates and need for repeated interventions. In addition, the evidence on renal preservation after endoscopic treatment is inconsistent and the long-term benefits are not assured, possibly due to the cumulative effects of repeated procedures and imaging during follow-up [170].

The use of flexible ureteroscopes with an external diameter < 9F is useful in the endoscopic management of UTUC [171].

Ablation is preferably performed with lasers; however, data regarding optimal laser type or settings are lacking. Although there is no evidence on optimal laser settings, excessive power should be avoided, as high power settings will generate heat and cause thermal injury of normal tissue [172].

Second-look URS after initial endoscopic treatment is recommended to ensure complete tumour resection and evaluate residual disease. Second-look URS should be performed within eight weeks following initial endoscopic treatment to assess for residual tumours or recurrence [167]. Other studies reported that up to nearly 50% of patients showed residual or recurrent disease during the second-look procedure, emphasising the value of early follow-up [173]. Therefore, early second-look URS plays a crucial role in optimising the outcomes of conservative treatment in UTUC by ensuring thorough tumour control.

### *7.1.3 Percutaneous antegrade access*

Percutaneous antegrade management can be considered for low-risk UTUC in the renal pelvis [165, 174]. This can also be offered for low-risk tumours that are inaccessible or difficult to manage by means of flexible retrograde URS, for example, in patients with urinary diversions. This approach is being used less in the wake of improved endoscopic possibilities with smaller sized ureteroscopes [166, 174]. Although rare, the risk of tumour seeding remains with percutaneous antegrade access [174].

### *7.1.4 Ureteral resection*

Segmental or distal ureterectomy and ureteral resection with adequate margins - ideally based on frozen section analysis - provides sufficient pathological specimens for staging and grading while preserving the ipsilateral kidney. Further direct anastomoses using either an end-to-end technique or ureteroneocystostomy are usually performed, but ileal-ureteral substitution or renal autotransplantation are also technically feasible, depending on the length of ureter removed [175, 176]. Segmental resection of the proximal two-thirds of ureter is associated with higher failure rates than for the distal ureter [177, 178]. Distal ureterectomy with ureteroneocystostomy for tumours in the distal ureter is reported with a low cumulative incidence of ipsilateral upper tract recurrence (0-18%) [179-181] compared to 25-85% after endourologic kidney sparing [170].

### *7.1.5 **Chemoablation***

A single-arm phase III trial including 71 patients with biopsy-proven low-grade UTUC measuring less than 15mm showed that the use of mitomycin-containing reverse thermal gel (UGN-101) instillations (six-weekly induction) in a chemoablation setting by means of a retrograde catheter to the renal pelvis and calyces was associated with a complete response (CR) rate in a total of 41 patients (58%) [182]. The most frequently reported all-cause adverse events (AEs) were ureteric stenosis in 31 (44%), urinary tract infection in 23 (32%), haematuria in 22 (31%), flank pain in 21 (30%), nausea in 17 (24%) and 19/31 (61%) reported ureteric stenosis requiring treatment. Among patients with CR, 29/41 (71%) received at least one maintenance instillation (median of six), and 23/41 (56%) remained disease free at one year [182]. Long-term outcomes remain uncertain [183].

### *7.1.6 **Adjuvant instillations***

#### 7.1.6.a Upper urinary tract

The antegrade instillation of BCG or mitomycin C in the upper urinary tract by means of percutaneous nephrostomy after complete tumour eradication has been studied for CIS after kidney-sparing management [184, 185]. Retrograde instillation through a single-J open-ended ureteric stent is also used [186]. Before both the antegrade and retrograde approach, a nephroureterogram must rule out ureteric obstruction or leakage, asses that there is no infection and ensure a low-pressure system to avoid pyelovenous backflow 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 [187, 188].

A systematic review and meta-analysis assessing the oncologic outcomes of patients with papillary (Ta-T1) UTUC or CIS of the upper urinary tract treated with kidney-sparing surgery and adjuvant endocavitary therapies (i.e. chemotherapeutic agents and/or BCG) did not find any difference between the method of drug administration (antegrade vs. retrograde vs. combined approach) in terms of recurrence, progression, CSS and OS. However, all included studies were underpowered and highly heterogeneous. Furthermore, the recurrence rates following adjuvant instillations are comparable to those reported in the literature in untreated patients, questioning their efficacy [189]. The analyses were based on retrospective small studies suffering from publication and reporting bias.

Further 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 [190]. Limited complications related to the instillations were reported, and the need for a retrograde pyelography before instillations are commenced to exclude contrast extravasation was confirmed.

#### 7.1.6.b Bladder

No data is currently available to support the use of bladder instillation of chemotherapy after kidney-sparing surgery, as available randomised controlled trials (RCTs) included only patients who received RNU.

### *7.1.7 **Recommendations for kidney-sparing management of localised low-risk upper urinary tract urothelial carcinoma***

| Recommendations | Strength rating |
|---|---|
| Offer kidney-sparing management as primary treatment option to patients with low-risk tumours. | Strong |
| Discuss both endoscopic management and distal ureterectomy in low-risk tumours of the distal ureter based on tumour characteristics and shared decision-making with the patient. | Strong |
| Perform second-look ureteroscopy within eight weeks following initial endoscopic management. | Weak |

## 7.2 Localised high-risk disease

### *7.2.1* ***Local treatments***

#### 7.2.1.a Radical nephroureterectomy

##### *7.2.1.a.1* ***Surgical approach***

Although the open approach has long been the standard [13], both laparoscopic and robot-assisted RNU can be used to treat high-risk UTUC, providing perioperative benefits such as decreased risk of complication and shorter hospital stay [191, 192]. In addition, equivalent oncological outcomes have generally been reported between the three procedures [191-193], except for a higher risk of intravesical recurrence after minimally invasive RNU [194]. It is worth noting that, although laparoscopic RNU was historically purported to provide inferior oncological outcomes [195] in locally advanced UTUC, this was not confirmed with the use of robotic RNU [194].

A meta-analysis of six retrospective comparative studies showed that the use of a retroperitoneal versus transperitoneal route at the time of laparoscopic RNU provides similar perioperative and oncological outcomes, except for a longer operative time and shorter recovery time to bowel function in the retroperitoneal group [196]. Similarly, retroperitoneal robotic RNU is safe and feasible to perform [197].

Regardless of the approach, RNU must be performed according to oncological principles to prevent tumour seeding:

- Perform *en bloc* removal of the kidney, ureter and bladder cuff.
- 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 [198].

##### *7.2.1.a.2* ***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 [32, 177, 199]. Several techniques have been described, including the transvesical, extravesical and endoscopic approaches with similar oncological outcomes regarding CSS. Uncertainty remains regarding their impact on intravesical recurrence [200, 201], with the endoscopic approach potentially affecting a higher risk of recurrence [201]. Several other techniques have been proposed to simplify distal ureter resection, including the pluck technique, stripping, transurethral resection of the intramural ureter, and intussusception, but none of these techniques have convincingly been shown to be equal to complete bladder cuff excision [33, 201].

##### *7.2.1.a.3* ***Lymph node dissection***

No high-level evidence is available to support the routine use of LND for upper tract tumours. However, template-based LND and its completeness may reduce the risk of local recurrence and improve CSS [202]. This could have a greater impact than the number of removed LNs [203]. Even in clinically [204] and pathologically [205] node-negative patients, LND may improve survival. Moreover, clinical tumour staging is inaccurate preoperatively. Provided the patient meets the strong criteria for high-risk disease (Figure 6.1), template-based LND could be offered to those who are scheduled for RNU, particularly given the low risk of major postoperative complications [206]. The templates for LND vary according to primary tumour location [202, 207, 208].

#### 7.2.1.b Kidney-sparing surgery

##### *7.2.1.b.1* ***Elective indications***

**Distal ureterectomy**

Distal ureterectomy - particularly with adequate surgical margins based on frozen section analysis - followed by ureteroneocystostomy may achieve equivalent long-term oncological outcomes and improved renal preservation as compared to RNU for high-risk UTUC located in the distal ureter [163, 164, 209, 210]. However, the risk of local- and intravesical recurrence is significantly higher following distal ureterectomy, emphasising the necessity of patient selection and close postoperative surveillance [211].

Two retrospective studies [212-215] including mainly high-risk patients, and one prospective study [216] including only high-risk patients, showed ipsilateral upper tract recurrence in 16-28% of cases after segmental ureterectomy, highlighting the need to weigh this risk against performing RNU on an individual patient basis. This procedure can be performed with concomitant LND.

**Ureterorenoscopy with laser ablation or segmental ureterectomy**

Patients with high-risk UTUC that harbour more favourable features (predominantly "weak" high-risk criteria, low-grade disease and no infiltrative features at imaging), cannot be systematically considered as an indication for RNU [217, 218]. Alternatively, the use of ureterorenoscopy with laser ablation or segmental ureterectomy may be proposed on a case-by-case basis if feasible.

#### *7.2.1.b.2 Imperative indications*

Ureterorenoscopy with laser ablation or segmental ureterectomy can be considered on a case-by-case basis for patients with high-risk UTUC and imperative kidney-sparing indications. This includes situations such as solitary kidney, bilateral UTUC, and even those harbouring high-grade disease and/or infiltrative features, but only in the presence of severe chronic kidney disease or any other comorbidity compromising the use of RNU. However, there is a greater risk of progression after kidney-sparing surgery for high- versus low-risk UTUC, with a direct impact on survival [163].

### *7.2.2 Perioperative treatments*

#### 7.2.2.a Neoadjuvant systemic treatments

#### *7.2.2.a.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 CR rates at RNU [219-223] with a direct impact on OS [224]. Moreover, 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 [222, 225-227].

No RCTs have been published yet, but prospective data from phase II trials showed that NAC based on cisplatin combination therapy was associated with a 14-19% pathological CR rate in high-grade and/or cT2-T4N0M0 UTUC [228, 229]. 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, resulting in an OS and CSS benefit compared with RNU alone [230]. A further systematic review and meta-analysis included 21 trials involving 14,117 patients with UTUC, comprising 1,983 patients who received NAC. Among those treated with NAC, 10% achieved a pathological CR and 42% experienced pathological downstaging; however, no survival benefit was demonstrated [231]. It is important to note that these findings are not conclusive, as the evidence is limited by significant bias and heterogeneity of the available data. If there is residual ≥ ypT2 and/or ypN+ disease after NAC and subsequent RNU, patients are likely to have a poorer prognosis [232]. Adjuvant immunotherapy should be discussed.

#### *7.2.2.a.2 Immunotherapy*

Only a small phase II study including ten patients with high-risk UTUC evaluated the efficacy of pembrolizumab in the neoadjuvant setting [233]. However, no pathological response was observed, and one treatment-related death was reported. Therefore, no evidence is currently available to support the use of neoadjuvant immunotherapy for high-risk UTUC.

#### *7.2.2.a.3 Chemoimmunotherapy*

The efficacy of the neoadjuvant combination of durvalumab with gemcitabine plus cisplatin (cohort 1) or carboplatin (cohort 2) before RNU has been evaluated in a negative phase II study showing pathological CR rates of 13% in those who received cisplatin and 5% in those who received carboplatin. These were both below the prespecified statistical hypotheses, although a final pathological stage < pT1 was found in 63% and 47% of patients included in cohort 1 and 2, respectively [234].

#### 7.2.2.b Perioperative intravesical instillations

#### *7.2.2.b.1 Adjuvant intravesical instillations*

The rate of bladder recurrence after RNU for UTUC is approximately 30% [32, 201]. Two prospective randomised trials [235, 236] and two meta-analyses [237, 238] have demonstrated that a single postoperative dose of intravesical chemotherapy (mitomycin C, pirarubicin) two to ten days after surgery reduces the risk of bladder tumour recurrence within the first years post-RNU in patients without a history of BC. Prior to instillation, a cystogram can be considered in case of concerns about drug extravasation. All studies showed a very low risk of AEs.

Based on current evidence, it is unlikely that additional instillations beyond one perioperative instillation of chemotherapy further substantially reduce the risk of intravesical recurrence [239]. 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 [240].

No data are currently available to support the use of bladder instillation of chemotherapy after kidney-sparing surgery, because available RCTs included only patients who received RNU.

#### *7.2.2.b.2 Other perioperative intravesical instillations*

Intravesical chemotherapy has been administered safely at the time of RNU prior to bladder cuff opening, removing the need for a postoperative cystogram but with low-level data for efficacy [241].

Given worldwide low compliance with the use of adjuvant bladder instillations after RNU, its efficacy has more recently been tested in the preoperative setting. A single bladder instillation of mitomycin C within three hours before RNU or segmental ureterectomy, combined with saline irrigation, provided a two-year intravesical recurrence rate of 24%, which was above the pre-specified threshold of 20% in a prospective study [242]. Nonetheless, a significant reduction in the risk of intravesical recurrence was observed in the subgroup of patients who did not receive diagnostic ureterorenoscopy before radical surgery using an historical cohort as a comparative group.

### 7.2.2.c Adjuvant treatments

#### *7.2.2.c.1 Systemic chemotherapy*

The POUT phase III multicentre prospective RCT (n = 261) evaluating the benefit of four cycles of adjuvant (AC) gemcitabine-platinum combination chemotherapy initiated within 90 days after RNU versus surveillance reported a significant improvement in DFS in patients with pT2-pT4, N (any) or positive (pT any, N1-3) M0 UTUC (three year DFS 71% vs. 50%; five year DFS 63% vs. 46%; HR: 0.54; 95% CI: 0.36-0.79; three- and five-year metastasis-free survival 19% improvement HR: 0.55; 95% CI: 0.36-0.77) [243]. Patients were stratified to gemcitabine/cisplatin or gemcitabine/carboplatin chemotherapy based on glomerular filtration rate (GFR) alone, with benefit seen irrespective of chemotherapy type. There was a non-significant trend towards improved OS (12% at three years), but because the study had met its primary endpoint of three-year DFS, the study closed early, leaving it underpowered for the secondary endpoint of OS. An updated analysis showed five-year DFS of 62% versus 45% (HR: 0.55; 95% CI: 0.38-0.80; p = 0.001) and mean restricted survival time was 18 months longer in the chemotherapy arm. Five-year OS was 66% versus 57% with univariate HR 0.68 (95% CI: 0.46; p = 0.49). Treatment effect was consistent across chemotherapy regimens (carboplatin or cisplatin) and disease stage [244]. The main potential limitation of using adjuvant chemotherapy is the concern that renal function may deteriorate after RNU, precluding cisplatin use in patients who could benefit from this [245, 246]. A review of perioperative predictors of decline in renal function after RNU showed three-month GFR levels of approximately 50mL/min [247]. With split dose and hydration, cisplatin may be considered in patients with a GFR down to 45mL/min. In addition, carboplatin can be used to GFR of 30mL/min. or above. Table 2 outlines the eligibility criteria for platinum chemotherapy.

In a retrospective study, histological subtypes of UTUC exhibited different survival rates and adjuvant chemotherapy was only associated with an OS benefit in patients with pure UC [248]. However, whilst histological subtypes of UTUC exhibit different survival rates in retrospective studies, adjuvant chemotherapy should be considered whenever UC is the dominant pathology.

**Table 2: Definitions of platinum-eligibility for systemic treatment of urothelial carcinoma** [2]

| **Platinum eligible** | | **Platinum ineligible** |
|---|---|---|
| **Cisplatin eligible** | **Carboplatin* eligible** | |
| ECOG PS 0-1 ***and*** GFR > 50-60mL/min. ***and*** audiometric hearing loss Grade < 2 ***and*** peripheral neuropathy Grade < 2 ***and*** cardiac insufficiency NYHA class < III | ECOG PS 2 *or* GFR 30-60mL/min. ***or*** not fulfilling other cisplatin-eligibility criteria | Any of the following:<br>• GFR < 30mL/min.<br>• ECOG PS > 2<br>• ECOG PS 2 *and* GFR < 60mL/min.<br>• Comorbidites > Grade 2 |

** Carboplatin is not indicated for neoadjuvant treatment.*
*ECOG PS = Eastern Cooperative Oncology Group performance status; GFR = glomerular filtration rate; NYHA = New York Heart Association.*

#### 7.2.2.c.2 *Systemic immunotherapy*

In a phase III, multicentre, double-blind RCT involving patients with high-risk muscle-invasive UC who had undergone radical surgery (pT3, pT4a or pN+), 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 [249]. The patient population predominantly consisted of BC patients post RC, with an additional smaller cohort of patients with UTUC post RNU (approx. 25%). The median RFS 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 AEs > 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. Nevertheless, the European Medicines Agency (EMA) approved nivolumab as monotherapy for the adjuvant treatment of patients with muscle-invasive UC and tumour cell PD-L1 expression > 1% who are at high risk of recurrence after radical surgery and who decline or are unfit for adjuvant chemotherapy [250]. A further study of 702 patients with UC treated with either RC or RNU, and with persistent high-risk features, were randomised to receive either adjuvant pembrolizumab or observation [251]. The DFS was significantly longer with pembrolizumab (29.6 months vs. 14.2 months); however, the number of patients with UTUC (25% of overall population) in the study was small and on subgroup analyses did not seem to benefit from adjuvant pembrolizumab [251].

A network meta-analysis suggests superior oncological benefit for adjuvant platinum-based chemotherapy over immune checkpoint inhibitors (CPIs) in patients treated with radical surgery for UTUC [252].

#### 7.2.2.c.3 *Radiotherapy*

Adjuvant radiation therapy has been suggested to control locoregional disease after surgical removal. The data remains controversial and insufficient for conclusions [253-256]. Moreover, its added value to chemotherapy remains questionable [255].

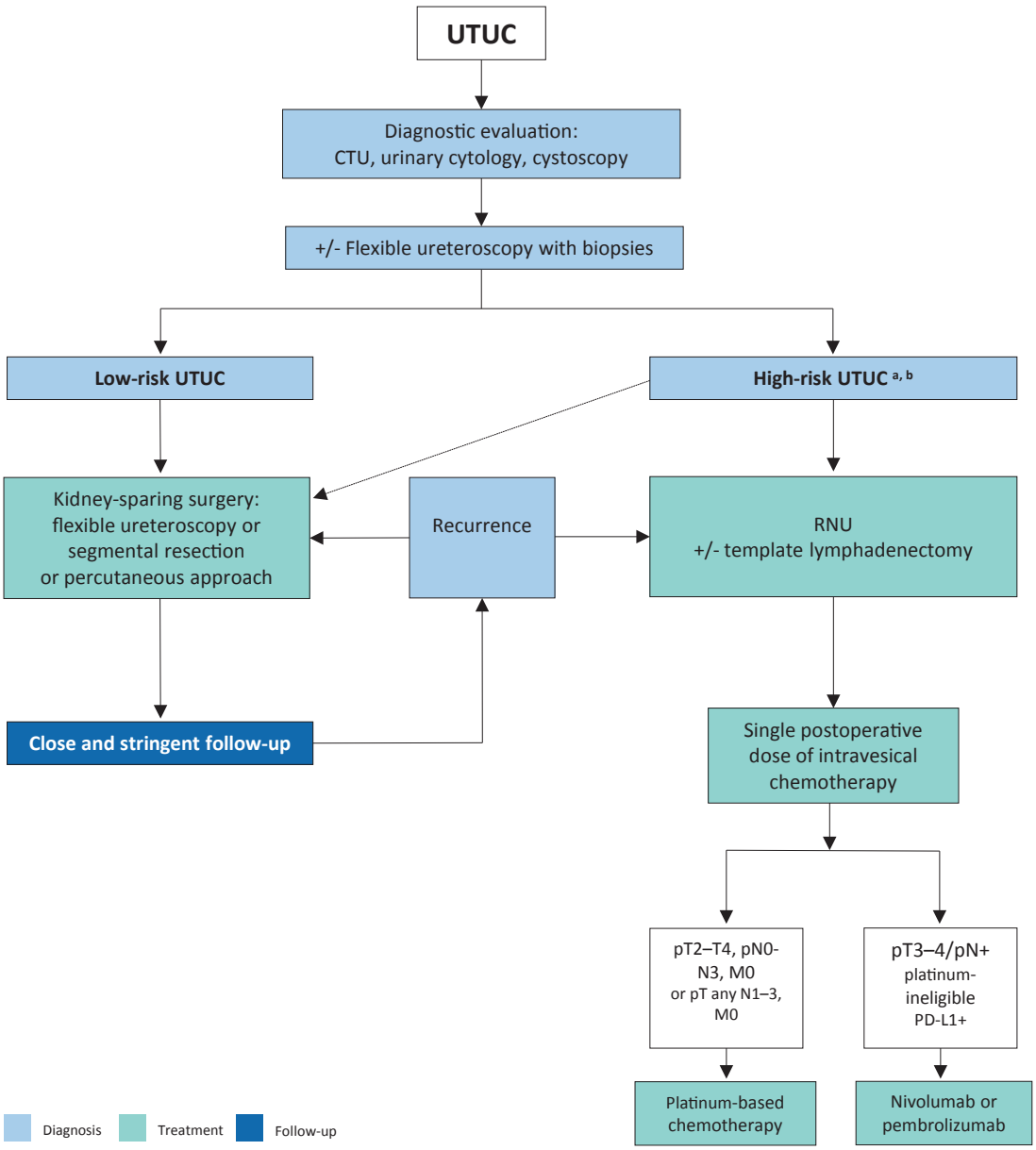
### 7.2.3 *Summary of evidence and recommendations for the management of high-risk non-metastatic upper urinary tract urothelial carcinoma*

| 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. | 2a |
| Failure to completely remove the bladder cuff increases the risk of BC recurrence. | 3 |
| Template-based LND may improve survival in muscle-invasive UTUC. | 3 |
| Postoperative platinum-based adjuvant chemotherapy improves DFS. | 1b |
| Single postoperative intravesical instillation of chemotherapy lowers the BC recurrence rate. | 1b |

| Recommendations | Strength rating |
|---|---|
| Discuss all patients with suspicion of upper urinary tract urothelial carcinoma (UTUC) on imaging in a multidisciplinary team meeting. | Strong |
| Perform radical nephroureterectomy (RNU) in patients with high-risk non-metastatic UTUC. | Strong |
| Use an open, laparoscopic or robotic approach to perform RNU in patients with high-risk non-metastatic UTUC. | Weak |
| Perform a template-based lymphadenectomy in patients with high-risk non-metastatic UTUC. | Weak |
| Offer adjuvant platinum-based chemotherapy after RNU to eligible patients with pT2-T4 and/or pN+ disease. | Strong |
| Deliver a postoperative bladder instillation of chemotherapy to lower the intravesical recurrence rate in patients without a history of bladder cancer. | Strong |
| Discuss adjuvant nivolumab with programmed death-ligand 1 (PD-L1) positive patients unfit for, or who declined, platinum-based adjuvant chemotherapy for ≥ pT3 and/or pN+ disease after previous RNU alone or ≥ ypT2 and/or ypN+ disease after previous neoadjuvant chemotherapy followed by RNU. | Weak |

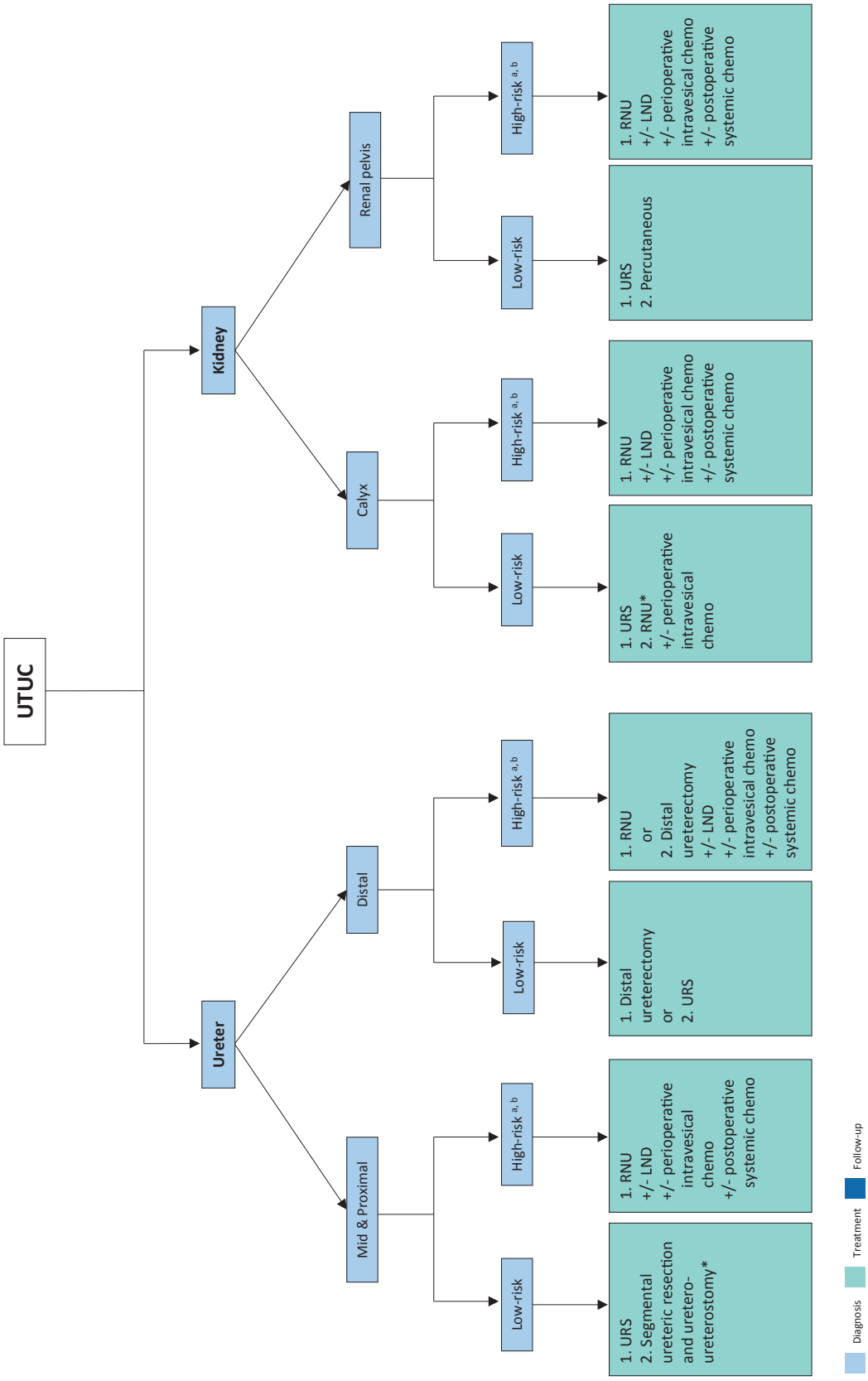
| | |
|---|---|
| Discuss adjuvant pembrolizumab with patients unfit for, or who declined, platinum-based adjuvant chemotherapy for ≥ pT3 and/or pN+ and/or positive margin disease after previous RNU alone or ≥ ypT2 and/or ypN+ and/or positive margin disease after previous neoadjuvant chemotherapy followed by RNU. | Weak |
| Offer distal ureterectomy to selected patients with high-risk tumours limited to the distal ureter. | Weak |
| Discuss kidney-sparing management of high-risk patients with imperative indication, on a case-by-case basis, in a shared decision-making process with the patient, despite the higher risk of disease progression. | Strong |

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




*a: In patients with solitary kidney, consider a more conservative approach.*
*b: In low-grade patients without invasive features, consider a more conservative approach.*
*CTU = computed tomography urography; PD-L1 = programmed death-ligand 1; RNU = radical nephroureterectomy; UTUC = upper urinary tract urothelial carcinoma.*

**Figure 7.2: Surgical treatment according to location and risk status**




*a: In patients with solitary kidney, consider a more conservative approach.*
*b: In low-grade patients without invasive features, consider a more conservative approach.*
*1 = first treatment option; 2 = secondary treatment option.*
**If not amendable 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 locoregional lymph node metastases*

Patients with clinical evidence of positive locoregional LNs which are surgically resectable fall in between localised and metastatic disease, and their treatment remains an area of debate. There are a number of options that could be considered based on published clinical trial data, but first-line treatment relies on systemic therapy. Induction platinum-based chemotherapy or enfortumab vedotin with pembrolizumab (EV + P) combination could be considered for these patients [257, 258]. Radical nephroureterectomy with template-based LND can be discussed in a multidisciplinary team for patients responding to initial systemic therapy [259]. A systematic review and meta-analysis of 15 studies showed that induction chemotherapy followed by RNU is associated with greater odds of pathological downstaging (response rate = 3.06; 95% CI: 2.48-3.77) and appears to prolong OS compared with RNU plus AC. However, the analysis is limited by the heterogeneity of the studies, fewer adjuvant trials, and differences in how nodal status was reported in the studies (e.g. type of nodal surgery) [259]. In addition, no data are available on the use of RNU combined with EV + P in these patients.

In patients whose cancer is stable or progresses, maintenance avelumab or second-line treatment can be offered, similar to distant metastatic disease. Unresectable cN+ patients should be treated as distant metastatic patients.

### *7.3.2 Distant metastases*

#### 7.3.2.a Systemic treatments - first-line setting

##### *7.3.2.a.1 Enfortumab vedotin plus pembrolizumab combination therapy*

For more than 23 years, despite multiple attempts with new agents and/or combinations of treatments, platinum-based chemotherapy remained the standard of care for previously untreated advanced or metastatic UC. In October 2023, the landscape changed dramatically with the EV302 phase III randomised multicentre study. This compared the nectin-4–directed antibody–drug conjugate EV + P with platinum-based combination chemotherapy (gemcitabine-cisplatin or gemcitabine-carboplatin. See Table 2 for the definition of cisplatin eligibility).

The study showed significant improvement in both PFS (HR: 0.45; 95% CI: 0.38-0.54) and OS (HR: 0.47; 95% CI: 0.38-0.58) with a response rate of 68% (vs. 44%) and a CR of 29%. Overall survival benefit was seen across subgroups regardless of cisplatin eligibility. The most common grade 3 or above treatment-related AEs of special interest included skin reactions (15.5%), peripheral neuropathy (6.8%) and hyperglycaemia (6.1%). The proportion of UTUC patients in this study was 25% and preplanned subgroup analysis showed benefit irrespective of tumour location [260].

Sequencing of treatment after EV + P is currently unclear and later-line treatments will depend on what agents the patient has previously received (Figure 7.3).

##### *7.3.2.a.2 Patients ineligible for enfortumab vedotin plus pembrolizumab and fit for cisplatin-based combination chemotherapy*

Upper tract UC and urothelial BC both respond to systemic platinum-based chemotherapy. Eligibility for platinum-based chemotherapy in the metastatic setting is based on the same criteria outlined in Table 2. 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 [261]. Therefore, cisplatin-containing combination chemotherapy is the standard treatment for advanced or metastatic UTUC in patients who are ineligible for EV + P [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 > 45mL/min [261].

The efficacy of immunotherapy using programmed death 1 (PD-1) 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 [262]. First-line immune CPIs or the combination of platinum-based chemotherapy with immune CPIs have not previously resulted in positive significant survival advantages and were thus not previously recommended [263-265]. These studies included both cisplatin and carboplatin combinations.

A phase III RCT in advanced/metastatic UC has now shown an OS benefit from the addition of nivolumab to chemotherapy (gemcitabine-cisplatin). Median OS was improved (21.7 months vs. 18.9 months; HR: 0.78; 95% CI: 0.63-0.96) as well as median PFS (7.9 months vs. 7.6 months; HR: 0.72; 95% CI: 0.59-0.88). Objective response rates were 57.6% compared with 43.1% for chemotherapy alone [266]. Although there is no subgroup analysis based on tumour position in this study, 12.6% of patients had UTUC.

#### *7.3.2.a.3 Patients ineligible for enfortumab vedotin plus pembrolizumab and unfit for cisplatin-based combination chemotherapy*

Carboplatin-based chemotherapy is recommended in patients unfit for cisplatin [2]. Carboplatin with gemcitabine is the preferred regimen [267], irrespective of PD-L1 status. In a critical re-analysis of RCTs comparing OS after cisplatin versus carboplatin-based regimens in advanced UC, cisplatin conferred a minor OS benefit compared to carboplatin [268].

#### *7.3.2.a.4 Maintenance therapy after first-line platinum-based chemotherapy*

Maintenance avelumab is recommended in patients with complete/partial response or stable disease after four to six cycles of platinum-based chemotherapy, given in the first line setting only. Data from a phase III RCT showed that the use of maintenance avelumab therapy after four to six cycles of gemcitabine plus cisplatin or carboplatin (started within ten 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 experience disease progression during, or responded to, first-line chemotherapy (HR: 0.69; 95% CI: 0.56-0.86) [269, 270]. 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) [271].

#### *7.3.2.a.5 Patients unfit for any combination therapy*

Pembrolizumab or atezolizumab are alternative choices for patients who are PD-L1 positive and not eligible or 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 [272]. 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 [273]. Median OS in the overall cohort was 15.9 months and treatment-related toxicity was in line with previous studies [264].

### 7.3.2.b Systemic treatments - later-line setting

Subsequent treatments depend on the type of treatment given in the first-line setting.

#### *7.3.2.b.1 Platinum-based chemotherapy*

Platinum-based chemotherapy should be the second-line treatment of choice if not received in the first-line setting. No data support the use of maintenance avelumab outside of the first-line setting. In addition, patients in this category are likely to have already received a CPI in the first-line setting, either in combination with enfortumab vedotin (EV) or as monotherapy.

#### *7.3.2.b.2 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) [274]. Responses were more frequent and durable for pembrolizumab compared to 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-positive tumours in patients with tumours that relapsed after platinum-based chemotherapy. The results of the trial failed to show a significant OS advantage of atezolizumab compared to second-line chemotherapy [275].

Other immunotherapies, such as nivolumab [276], avelumab [277, 278] and durvalumab [279], have shown objective response rates ranging from 17.8% [279] to 19.6% [276], 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 [278].

The immunotherapy combination of nivolumab plus ipilimumab has shown significant antitumour activity with objective response rate up to 38% in a phase I/II multicentre trial including 78 patients with metastatic UC experiencing disease progression after platinum-based chemotherapy [280]. Although UTUC patients were included in this trial, no subgroup analysis was available. A real-world study of 235 patients with UTUC treated with pembrolizumab after progression on first-line platinum-based chemotherapy confirmed objective response rate of 32% [281]. Other immunotherapy combinations may be effective in the second-line setting, but data are currently limited [282].

#### *7.3.2.b.3* ***Novel agents***

**Fibroblast growth factor receptors inhibition**

Erdafitinib, a pan-*FGFR* tyrosine kinase inhibitor of *FGFR* 1-4, was associated with a 40% radiological response rate according to the Response Evaluation Criteria in Solid Tumours (RECIST) 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 (*FGFR* 2/3 fusions or *FGFR* 3 mutations) [136]. This study included 23 UTUC patients with visceral metastases showing a 43% radiological response rate. The subsequent phase III Thor trial randomised 266 patients with advanced UC who had similar mutations and had experienced disease progression after 1-2 lines of previous treatment, to treatment with either erdafitinib or investigators choice of chemotherapy (vinflunine or docetaxel). Significant improvements in median OS (4.3 months; HR: 0.64; 95% CI: 0.47-0.88), PFS (2.9 months; HR: 0.58; 95% CI: 0.44-0.78) and a 36% risk reduction in death were observed. In this study, 33.5% of patients had UTUC [283]. A potentially greater impact of *FGFR* 3 targeting agents is anticipated, because the rate of activating alterations of *FGFR* 3 is higher in UTUC than in BC [284]. UTUC patients should be tested for *FGFR* alterations (*FGFR* 2/3 mutations or *FGFR* 3 fusions) prior to erdafitinib treatment. Early testing for *FGFR* 2/3 alterations, mutations and deletions should be considered for patients presenting with advanced/metastatic UTUC (Section 5.7).

**Antibody drug conjugates**

A phase II study enrolled 89 patients (43% of whom had UTUC) with cisplatin-unfit metastatic UC experiencing disease progression after therapy with PD-1 or PD-L1 inhibitors. All patients received the antibody-drug conjugate EV. The objective radiological response rate (RECIST) was 52%, of which 20% of patients achieved CR [285]. In a phase III trial of EV 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, EV significantly prolonged survival as compared to standard chemotherapy (median OS 12.88 vs. 8.97 months) [286].

In an open-label phase II trial, a total of 108 patients with metastatic UC who progressed after platinum-based chemotherapy and CPIs 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 UTUC was not mentioned in the publication [287].

A preplanned 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 CPIs [288]. Median PFS was 3.15 months on ramucirumab/docetaxel versus 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, because this analysis is limited by patient numbers and an imbalance in the treatment arms.

### 7.3.2.c **Surgery**

#### *7.3.2.c.1* ***Radical nephroureterectomy***

Data regarding RNU in the metastatic setting are lacking with evidence mainly limited to retrospective observational studies [289-291].

Although evidence remains very limited, RNU may be associated with CSS [290, 292-294] and OS benefit in selected patients, especially those fit enough to receive cisplatin-based chemotherapy [289, 290]. It is noteworthy that these benefits may be limited to those patients with only one metastatic site [290]. 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 [24, 295].

#### *7.3.2.c.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 [296-300]. 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.

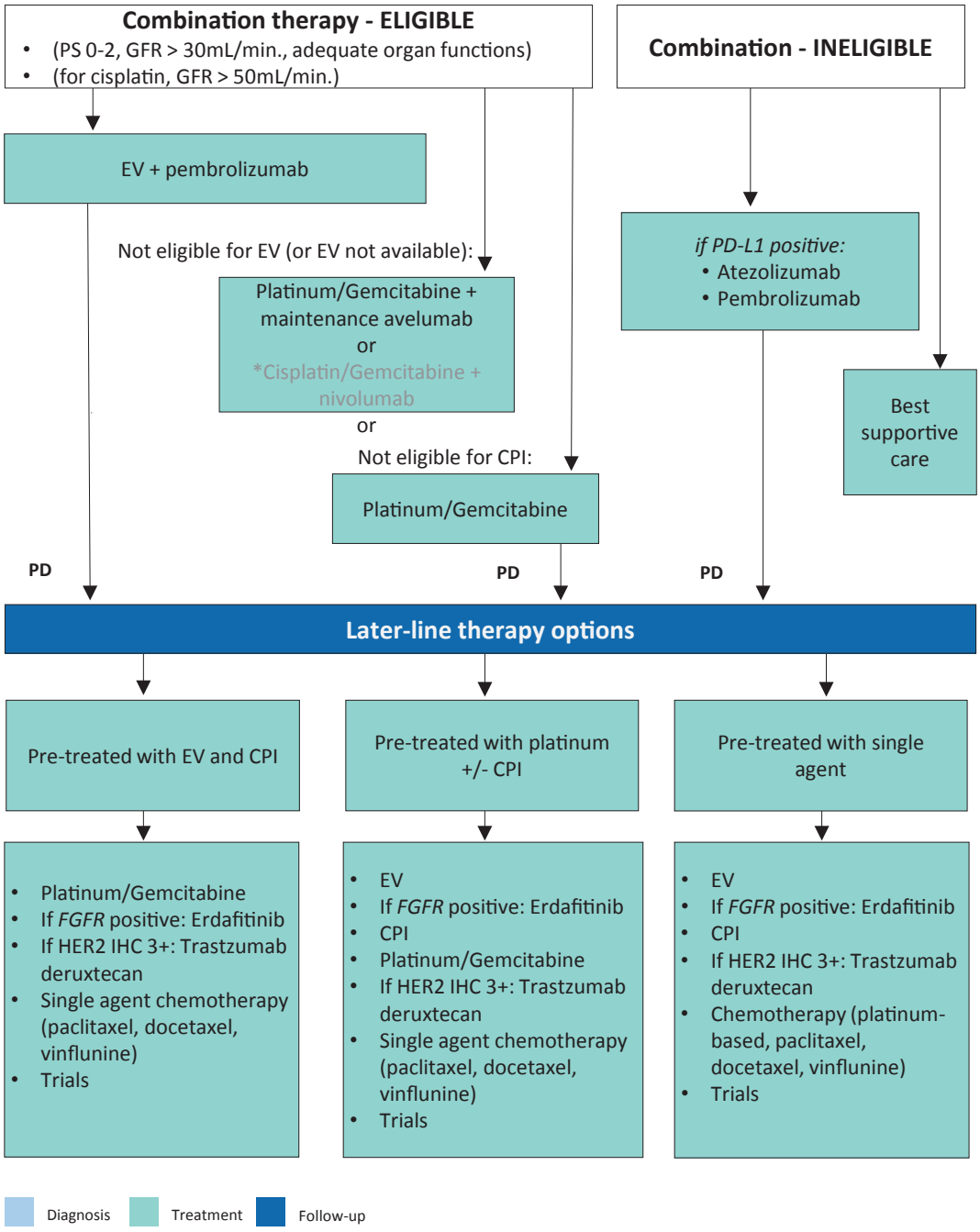
### *7.3.3 **Summary of evidence and recommendations for the treatment of metastatic upper urinary tract urothelial carcinoma***

| **Summary of evidence** | **LE** |
|---|---|
| Enfortumab vedotin plus pembrolizumab offers an OS benefit compared to gemcitabine-cisplatin in the first-line setting. | 1b |
| 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 and who are ineligible for EV + P. | 1b |
| Cisplatin-containing combination chemotherapy in combination with nivolumab offers a survival advantage compared with chemotherapy alone in the first-line setting. | 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 four to six cycles of gemcitabine plus either cisplatin or carboplatin. | 1b |
| Pembrolizumab, a PD-1 inhibitor, has been approved for patients who have experienced disease progression during or after previous platinum-based chemotherapy and did not receive previous immune therapy, based on the results of a phase III trial. | 1b |
| Nivolumab, a PD-1 inhibitor, has been approved for patients who have experienced disease progression during or after previous platinum-based chemotherapy and did not receive previous immune therapy, based on the results of a phase II trial. | 2a |
| Pembrolizumab, a PD-1 inhibitor, 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 |
| Atezolizumab, a PD-L1 inhibitor, 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 improved OS in platinum-refractory patients with locally advanced or metastatic UC and *FGFR* DNA genomic alterations (*FGFR* 2/3 mutations or *FGFR* 3 fusions). | 1b |
| 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 RNU can improve quality of life by controlling symptomatic disease. | 3 |
| Radical nephroureterectomy could confer a survival benefit in highly selected patients with metastatic UC, for example, after response to platinum-based combination chemotherapy with limited metastatic burden. | 4 |

| Recommendations | Strength rating |
|---|---|
| Offer EV + P as first-line treatment to patients with advanced/metastatic disease. | Strong |
| ***First-line treatment for platinum-eligible patients who are unsuitable/ineligible for EV + P*** | |
| Offer platinum combination chemotherapy to platinum-eligible patients. | Strong |
| Offer cisplatin-based chemotherapy with gemcitabine-cisplatin plus nivolumab in cisplatin-eligible patients. | Weak |
| Offer cisplatin-based chemotherapy with gemcitabine/cisplatin or HD-MVAC to cisplatin-eligible patients. | Strong |
| Offer gemcitabine/carboplatin chemotherapy to cisplatin-ineligible patients. | Strong |
| Offer maintenance avelumab to patients who did not have disease progression after four to six cycles of platinum-based combination chemotherapy. | Strong |
| ***First-line treatment in patients ineligible for any combination therapy*** | |
| Offer CPIs pembrolizumab or atezolizumab to patients with PD-L1 positive tumours. | Weak |
| ***Later lines of treatment*** | |
| Offer platinum-based combination chemotherapy as second-line treatment of choice if not received in the first-line setting. | Strong |
| Offer CPI (pembrolizumab) to patients with disease progression during or after platinum-based combination chemotherapy for metastatic disease who did not receive maintenance avelumab. | Strong |
| Offer EV 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 |
| Offer erdafitinib as an alternative subsequent-line therapy to patients:<br>• previously treated with platinum-containing chemotherapy<br>• who had disease progression during or after treatment with a PD-1 or PD-L1 inhibitor<br>• who harbour *FGFR* DNA genomic alterations (*FGFR* 2/3 mutations or *FGFR* 3 fusions). | Strong |
| Only offer vinflunine to patients with 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 RNU as a palliative treatment to symptomatic patients with resectable locally advanced tumours. | Weak |

*CPI = checkpoint inhibitors; DNA = deoxyribonucleic acid; EV = enfortumab vedotin; EV + P = enfortumab vedotin plus pembrolizumab; FGFR = fibroblast growth factor receptors; HD-MVAC = high-dose intensity methotrexate, vinblastine, adriamycin plus cisplatin; PD-1 = programmed death-1; PD-L1 = programmed death-ligand 1; RNU = radical nephroureterectomy.*

**Figure 7.3 Flowchart for the management of metastatic upper urinary tract urothelial carcinoma**




**In view of lack of subgroup analysis data for upper urinary tract urothelial carcinoma.*
*CPI = checkpoint inhibitor; EV = enfortumab vedotin; FGFR = fibroblast growth factor receptor; GFR = glomerular filtration rate; PD = programmed death; PD-L1 = programmed death-ligand 1; PS = performance status.*

# 8. FOLLOW-UP

The objectives of 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/or distant metastases. 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 previous RNU for low-risk tumours, bladder follow-up should adopt the NMIBC follow-up protocol for low-risk disease, namely, a cystoscopy at three months postoperatively, a subsequent cystoscopy nine months later and yearly cystoscopies for five years [301]. Screening for metastases during follow-up is not mandatory. Due to the low risk of contralateral upper tract recurrence, routine imaging should be discussed on an individual basis [302].

When RNU has been performed for high-risk tumours, stringent follow-up is mandatory to detect metachronous bladder tumours (probability increases over time [303]), local recurrence and distant metastases. The risk of bladder recurrence is higher in patients with a previous history of BC compared to those without, indicating the need for more intensive cystoscopy follow-up [304]. The risk of bladder recurrences and other-site recurrences decreases significantly four years after RNU, suggesting that less vigorous annual cystoscopies and cross-sectional imaging including CT urographies may apply [304]. As for other non-urothelial recurrences after RNU, most lung metastases develop within two years of surgery [305], supporting a more intensive use of chest CT during this period.

After kidney-sparing management for low-risk UTUC, and where no subsequent upstaging or upgrading occurred after the early second-look ureteroscopy after six to eight weeks [167], or was found in the resection specimen after segmental ureteric resection, cystoscopy and CT urography should be carried out at three and six months, and then yearly for five years. The risk for bladder recurrences beyond five years is low after endoscopic treatment and segmental ureterectomy [306, 307].

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 upper urinary tract requires careful and long-term follow-up due to the high risk of disease recurrence [171, 308, 309] and progression following RNU, even beyond five years [310]. The risk of bladder recurrences is likely higher in patients with a previous history of BC prior to segmental ureterectomy [216, 305].

Surveillance regimens are based on CT urography, cystoscopy and urinary cytology [303, 311]. There are, however, several unanswered questions related to the optimal follow-up of patients treated for both low-risk and high-risk UTUC, some of which are:

- What is the added value of new urinary markers compared to cytology in voided urine samples in high-risk patients [115]?
- What is the effect of the Paris System on sensitivity and specificity of voided and selective urinary cytology during follow-up of UTUC in high-risk tumours [312]?
- If adjuvant upper tract instillations have been administered after endourologic kidney-sparing management, will that allow for less vigorous follow-up?
- What is the role of ureteroscopies of the ipsilateral upper urinary tract during follow-up after endourologic kidney-sparing treatment versus CT urography and voided urinary cytology?

Additionally, it is not known how patients with Lynch syndrome, with and without UTUC, should be screened or followed long-term, given the inadequacy of surveillance based on urinalysis for non-visible haematuria [313] and urine cytology [314], particularly in those individuals who are *MSH2* mutation carriers [315] and those who have already developed 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 upper urinary tract urothelial carcinoma

| Summary of evidence | LE |
|---|---|
| Follow-up should be based on risk stratification and the type of treatment. | 3 |

| Recommendations | Strength rating |
|---|---|
| ***After radical nephroureterectomy (RNU)*** | |
| **Low-risk tumours** | |
| Perform cystoscopy at three months. If negative, perform subsequent cystoscopy nine months later and then yearly for five years. | Weak |
| **High-risk tumours** | |
| In patients with a prior history of non-muscle-invasive bladder cancer (NMIBC), perform cystoscopy and voided urinary cytology at three months. If negative, repeat subsequent cystoscopy and cytology every three months for a period of two years, and every six months thereafter until five years, and then yearly. | Weak |
| In patients without a prior history of NMIBC, perform cystoscopy and voided urinary cytology at three months. If negative, repeat subsequent cystoscopy and cytology every six months for a period of two years and every year thereafter until five years. | Weak |
| Perform computed tomography (CT) urography and chest CT every six months for two years, and then yearly. | Weak |
| ***After kidney-sparing management*** | |
| **Low-risk tumours** | |
| For bladder follow-up, perform cystoscopy at three and six months and then yearly for five years. | Weak |
| For upper tract follow-up, after negative second-look ureteroscopy (URS), perform CT urography at three and six months and then yearly for five years with or without URS*. | Weak |
| **High-risk tumours** | |
| In patients with a prior history of NMIBC, perform cystoscopy and voided urine cytology at three months. If negative, repeat subsequent cystoscopy and cytology every three months for two years, then every six months for five years, and then yearly. | Weak |
| In patients without a prior history of NMIBC, perform cystoscopy and voided urine cytology at three months. If negative, repeat subsequent cystoscopy and cytology every six months for two years, then every year for five years (same follow-up schedule as for high-risk tumours after RNU). | Weak |
| For upper tract follow-up, after negative second-look URS, perform cross-sectional imaging urography and URS at three and six months and then CT urography every six months for two years and then every year for five years, with or without URS*. | Weak |

**The role of URS of the ipsilateral upper urinary tract during follow-up after endourologic kidney-sparing treatment versus CT urography and voided urinary cytology is unknown.*

# 9. QUALITY INDICATORS FOR THE MANAGEMENT OF UPPER URINARY TRACT UROTHELIAL CARCINOMA

Evidence-based Quality Indicators (QIs) and Quality Performance Indicators (QPIs) are designed to be surrogates of good practice and, consequently, of outcomes. These evidence-based QIs and QPIs allow for the gap between efficacy and effectiveness to be narrowed, i.e. being able to bring research evidence and Guidelines recommendations into real world practice by improving compliance to them [316]. They also permit objective monitoring of the quality of care and thus facilitate quality control and service improvements.

No QIs have been proposed for the overall management of UTUC. These QIs remain to be defined for the diagnosis of UTUC as well as the treatment of low-risk or metastatic disease and further follow-up. However, several QIs have been proposed for the perioperative management of high-risk patients treated with RNU, including complete bladder cuff removal, concomitant tailored-based LND, early postoperative single bladder instillation of chemotherapy and risk-adapted delivery of neoadjuvant or adjuvant systemic treatments [317].

In addition, the achievement of an RNU-specific pentafecta, including negative surgical margins, complete bladder cuff removal, the absence of haematological or major complication, and the absence of postoperative recurrence at 12 months, has been shown to provide higher five-year OS and CSS rates [318]. Similar results have been observed with the achievement of an RNU-specific tetrafecta, including negative surgical margins, complete bladder cuff removal, Guidelines-based LND, and the absence of postoperative recurrence at 12 months [319]. Finally, in a population-based study, a hospital volume of > six patients per year treated with RNU was associated with improvement of short-term outcomes (30- and 90-day mortality) and overall long-term survival [320].

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# 11. CONFLICT OF INTEREST

All members of the NMIBC and UTUC Guidelines working group 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 provided below and is also publicly available on the EAU website: https://uroweb.org/guidelines/upper-urinary-tract-urothelial-cell-carcinoma/panel.

This Guidelines document was developed with the financial support of the EAU. No external sources of funding and support have been involved. The EAU is a non-profit organisation, and funding is limited to administrative, travel and meeting expenses. No honoraria or other reimbursements have been provided.

Disclosures: The EAU Guidelines Office certifies that all conflicts of interest, including specific financial interests and relationships and affiliations relevant to the subject matter or materials discussed in the manuscript (eg, employment/ affiliation, grants or funding, consultancies, honoraria, stock ownership or options, expert testimony, royalties, or patents filed, received, or pending), are the following:

A. Masson-Lecomte (Chair) reported receiving company speaker honoraria fees from Astellas Pharma, BMS, Ferring, Medac and MSD; attending advisory board meetings as a company consultant to Janssen Global Bladder Cancer and Pfizer; being an academy faculty advisor to Photocure; receiving grants or research support from Ferring and Ipsen Pharma; and participation in clinical trials by Janssen Cilag and MSD. J. Baard reported receiving company honoraria or consultation fees from Astellas, Boston Scientific, Coloplast, Cook, GSK, Olympus, Storz, TSC life and UroGen Pharma; and receiving fellowship or travel grant support from Astellas. A. Birtle reported receiving company speaker honoraria fees from Johnson & Johnson, Astellas, MSD, Merck, Accord and Bayer; serving as a company consultant to MSD, Bayer, Macrogenics and Ipsen; serving on the advisory board of Macrogenics, Johnson & Johnson, Astellas, Merck and AstraZeneca; being a trustee/medical advisor to Fight Bladder Cancer; and being a member of the ESMO Educational Committee. E.M. Compérat reported serving as a company consultant to Daiitchi, Johnson & Johnson and Astra. J.L. Dominguez-Escrig reported receiving company speaker honoraria fees from Presurgy, BMS and Angiodynamics; attending advisory board meetings as a company consultant to Astellas; and participation in clinical trials by Janssen, Arquer, Physion, Combat BRS, Ipsen, Storz, Uromonitor, Fidia Farmaceutici and Angiodynamics. P. Gontero reported receiving company speaker honoraria fees from Merck, Janssen and Medac; serving as a company consultant to Ferring, Medac, Pfizer, Photocure, MSD and AstraZeneca; receiving grants or research support from Intuitive Surgical, Astellas and Ferring; acting as chair of the institution for clinical trials by Johnson & Johnson; and participation in clinical trials by Ferring and Catalym. P. Mariappan reported receiving company speaker honoraria fees from BMS, Janssen Cilag, Medac Pharma and Photocure; serving on the core committee of the International Bladder Cancer Group; receiving grants or research support from Nucleix; and participation in clinical trials by Nucleix. B. Pradere reported receiving company honoraria or consultation fees from Astellas Pharma, Ferring, Johnson & Johnson, Laboratoires MSD, Ipsen Pharma and Photocure; serving as a company consultant to Johnson & Johnson; and participation in clinical trials by AstraZeneca and Johnson & Johnson. B.P. Rai reported receiving company speaker honoraria fees from Ipsen, Janssen-Cilag and Bayer. B.W.G. van Rhijn reported receiving advisory board meeting company consultation fees from Cepheid. T. Seisen reported receiving company honoraria or consultation fees from ADACAP, Astellas, Bayer, BMS, Ipsen, Janssen, MSD, Pfizer and VitaDX; receiving grants or research support from Institut de Recherche Servier and Ipsen; receiving fellowship or travel grant support from Institut de Recherche Servier; and participation in clinical trials by AstraZeneca, Ferring, Janssen and Roche. S.F. Shariat reported receiving company honoraria or consultation fees from Astellas Pharma, AstraZeneca, Bayer Austria, BMS, Ferring, Johnson & Johnson, MSD and Pfizer; and is the owner of four patents. J. Teoh reported receiving company speaker honoraria fees from Ferring Pharmaceuticals, Olympus Corporation and Astellas; serving as a company consultant to Johnson & Johnson, Ferring and MSD; receiving grants or research support from Olympus Corporation; and participation in clinical trials by AstraZeneca, BMS and Johnson & Johnson. E.N. Xylinas reported receiving company honoraria or consultation fees from Pfizer, Astellas, AstraZeneca, Boston Scientific, BMS, Ferring, Johnson & Johnson, Merck, MSD and Pfizer; receiving grants or research support from AstraZeneca, Boston Scientific and Ferring; participation in clinical trials by AstraZeneca, Janssen Cilag, MSD and Pfizer; and serving in a leadership role for the Association Française d'Urologie. D. D'Andrea reported receiving company speaker honoraria fees from Merck, Photocure, Olympus and Pfizer; and serving as a company consultant to Cepheid. O. Capoun reported receiving company honoraria or consultation fees from Accord Healthcare, Astellas Pharma, AstraZeneca, Bayer, Janssen and Novartis; and participation in clinical trials by Bayer and Janssen. M. Moschini reported receiving company honoraria or consultation fees from Janssen Cilag, Medac Pharma, Photocure and Johnson & Johnson; and serving as a company consultant to Pfizer Italiana. F. Soria reported receiving company honoraria or consultation fees from Medac Pharma, Johnson & Johnson, Photocure, Pfizer, AstraZeneca and Cepheid; and participation in clinical trials by Fidia Farmaceutici, Janssen, Steba biotech and Catalym. F. Liedberg, V. Soukup, E. Fiorini and R. Wood have nothing to declare.

# 12. CITATION INFORMATION

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