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 [1], muscle-invasive and metastatic bladder cancer (MIBC) [2], and primary urethral carcinoma [3].

It must be emphasised that clinical guidelines present the best evidence available to the experts, but following guideline recommendations will not necessarily result in the best outcome. Guidelines can never replace clinical expertise when making treatment decisions for individual patients, but rather help to focus decisions - also taking personal values and references/individual circumstances of patients into account. Guidelines are not mandates and do not purport to be a legal standard of care.

1.2 Panel composition

The European Association of Urology (EAU) Guidelines Panel on NMIBC and 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). All involved in the production of this document have submitted potential conflict of interest statements, which can be viewed on the EAU website Uroweb: https://uroweb.org/guidelines/upper-urinary-tract-urothelial-cell-carcinoma/panel/.

1.3 Available publications

A quick reference document, the Pocket Guidelines, is available online and in print. This is an abridged version which may require consultation together with the full text version. Several scientific publications are available, the most recent scientific summary was published in 2021 [4]. All documents are accessible through the EAU website: https://uroweb.org/guideline/upper-urinary-tract-urothelial-cell-carcinoma/.

A 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 extended guidelines.

1.4 Publication history & summary of changes

The first EAU Guidelines on UTUC were first published in 2011. Standard procedure for EAU Guidelines includes an annual assessment of newly published literature in the field to guide future updates. The 2025 UTUC Guidelines presents an update of the 2024 version.

1.4.1 Summary of changes

For the 2025 UTUC Guidelines, new and relevant evidence was identified, collated and appraised through a structured assessment of the literature for all sections of the Guidelines. This resulted in the inclusion of 17 updated studies across the Guidelines. Key changes include:

- Significant changes to the recommendations for the diagnosis of UTUC in section 5.7.
- Complete revision of Chapter 6 Risk stratification.
- Complete revision of section 7.1.2 Ureteroscopy.
- The addition of two new recommendations to section 7.1.7 related to kidney-sparing management of localised low-risk UTUC.
- Complete revision of section 7.2.1.1 Surgical approach for radical nephroureterectomy.
- The addition of two new recommendations to section 7.2.5 related to management of high-risk non-metastatic UTUC.
- Review and adaption of the section 8.1 recommendations for the follow-up of UTUC.
- Addition of a new chapter addressing quality indicators for the management of UTUC, chapter 9.

2. METHODS

2.1 Data identification

For the 2025 UTUC Guidelines, new and relevant evidence has been identified, collated, and appraised through a structured assessment of the literature. The search was restricted to articles published between May 1st 2023 and May 1st 2024. 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 302 unique records were identified, retrieved, and screened for relevance.

Excluded from the search were basic research studies, case series, reports, and editorial comments. The publications identified were mainly retrospective, including some large multicentre studies. Owing to the scarcity of randomised data, articles were selected based on the following criteria: evolution of concepts, intermediate- and long-term clinical outcomes, study quality, and relevance. Older studies were only included if they were historically relevant.

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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 which accompany each guideline statement, addresses a number of key elements:

1. the overall quality of the evidence which exists for the recommendation [5];
2. the magnitude of the effect (individual or combined effects);
3. the certainty of the results (precision, consistency, heterogeneity and other statistical or study related factors);
4. the balance between desirable and undesirable outcomes;
5. the impact 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 online: 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 (UC) is the second most common urological malignancy in developed countries [7]. They 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 upper tract urothelial carcinomas (UTUC) account for only 5-10% of UCs with an estimated annual incidence in Western countries of almost 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 men [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]. This was confirmed by a meta-analysis pooling 44 studies that 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 vs. BC has been confirmed in population-based studies from Germany and England suggesting that muscle-invasive UTUC represents approximately half of incident cases in recent years [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* of the upper tract is between 11% and 36% [8].

Concurrent BC is present in 17% of UTUC cases [20] whilst a prior history of BC is found in 41% of American men but in only 4% of Chinese men [21]. In high-risk NMIBC patients treated with intravesical bacillus Calmette-Guérin (BCG) the prevalence of UTUC ranged from 7.5% to 25% [22-24] and from 3% to 5% in those with MIBC treated with radical cystectomy [25, 26].

Following treatment for UTUC, recurrence in the bladder occurs in 29% of UTUC patients, depending on patient-, tumour- and treatment-specific characteristics [27] compared to a 2–5% recurrence rate in the contralateral upper tract [28].

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

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, 30]. 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 fold [31-33].

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 [34-36]. However, it is estimated that less than 10% of individuals exposed to aristolochic acid develop UTUC [36]. Aristolochic acid has also been linked to BC, renal cell carcinoma, hepatocellular carcinoma, and intrahepatic cholangiocarcinoma [37]. Following bioactivation, aristolochic acid reacts with genomic DNA to form aristolactam-deoxyadenosine adducts [38]; these lesions persist for decades in target tissues, serving as robust biomarkers of exposure [39]. These adducts generate a unique mutational spectrum, characterised by A>T transversions located predominately on the non-transcribed strand of DNA [37, 40]. Two routes of exposure to aristolochic acid are known: (i) environmental contamination of agricultural products by aristolochia plants, as reported for Balkan endemic nephropathy [41]; and (ii) ingestion of aristolochia-based herbal remedies [42, 43]. Aristolochic acid-associated UTUC is more common in females [44, 45], 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 [46, 47]. Arsenic mitigation from drinking water in Taiwan has also been shown to reduce the incidence of UTUC in a large population-based study [48]. Consumption of arsenic in drinking water and aristolochia-based herbal remedies together appears to have an additive carcinogenic effect [49].

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 evidenced a significantly higher risk of UTUC in ever drinkers compared to never drinkers (OR: 1.23; 95% CI: 1.08–1.40, $p = 0.001$). Compared to never drinkers, the risk threshold for UTUC was > 15 g of alcohol/day. A dose-response has been observed [50].

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 MLH1, MSH2, MSH6 or PMS2. After colorectal and endometrial cancers, UTUC is the 3rd most common malignancy in the Lynch syndrome spectrum [51]. 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 can be found in 1%-3% of patients with UTUC [52].

From a genetic perspective, the majority of tumours develop in MSH2 and MSH6 mutation carriers [53]. 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 MLH1, MSH2, MSH6 or PMS2 in immunochemistry, which can be responsible for a microsatellite instability identified using the PCR method.

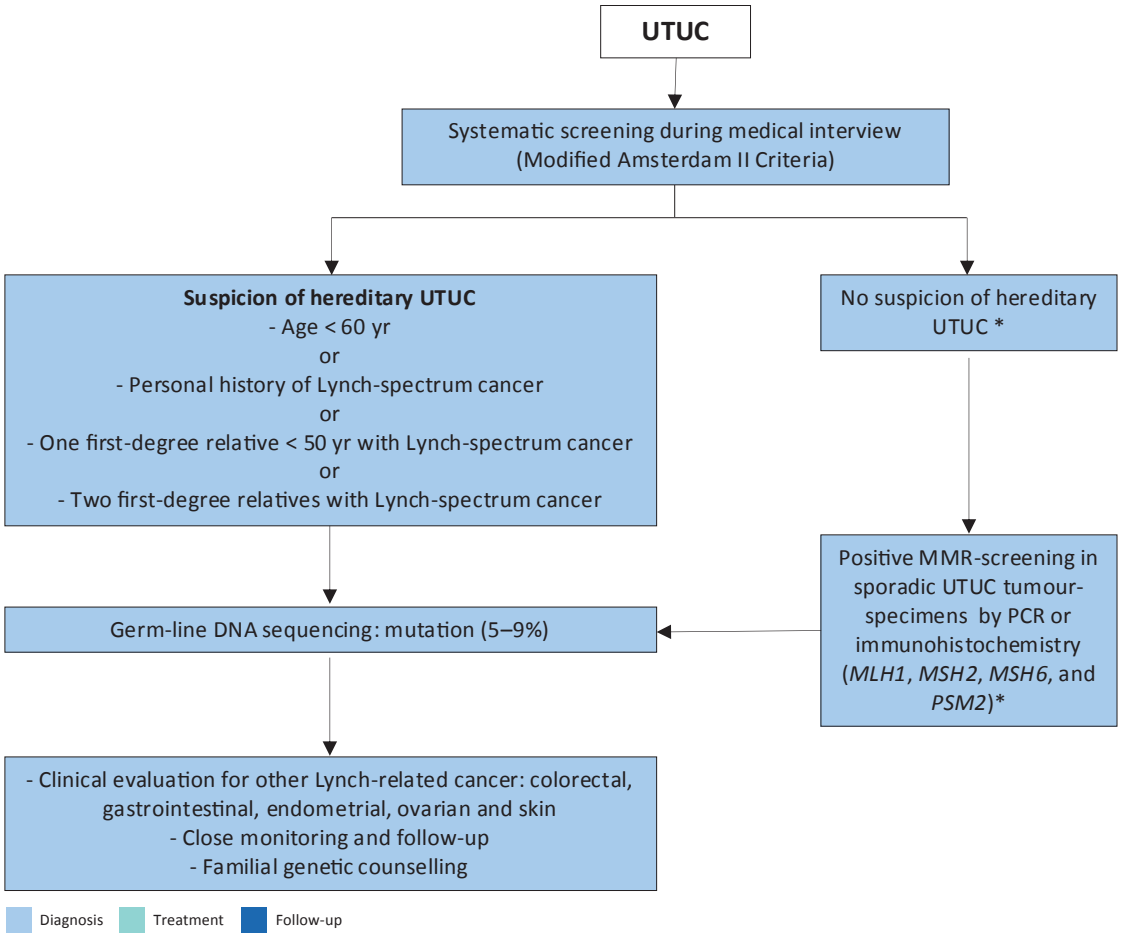
From a clinical perspective, although the PREMM5 model has been developed to estimate the cumulative probability of an individual to carry a germline mutation related to the Lynch syndrome [54], the Amsterdam II criteria remains predominantly used to identify families that are at increased risk of Lynch syndrome [55]. The latter includes:

1. At least three relatives with a Lynch-associated cancer (colorectal, endometrium, small bowel or UTUC);
2. A first degree relative to the other two;
3. At least two successive affected generations;
4. At least one relative diagnosed before the age 50;
5. Exclusion of familial adenomatous polyposis in the colorectal cancer cases;
6. 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 [56].

Another UTUC-specific study has suggested that an age < 60 at initial diagnosis and a personal history of any other Lynch-related malignancy could be both associated with an increased risk of Lynch syndrome in these patients [57]. A simplified screening tool for UTUC patients has been proposed including these two criteria associated with two others deriving from the Amsterdam II criteria and including one-first degree relative with Lynch-related cancer diagnosed before 50 and two first-degree relatives with Lynch-related cancer regardless of age [58]. Using this simplified screening tool, the proportion of UTUC patients with a suspicion of Lynch-related disease could be more than 20% [58]. Importantly, patients with UTUC who are identified at high risk for Lynch syndrome based on clinical criteria should undergo germline DNA sequencing and family counselling [59, 60] (Figure 3.1). Nonetheless, given the limited diagnostic performance of clinical criteria, UTUC patients without suspicion for genetic predisposing factors could be tested for MSI or dMMR using PCR or immunochemistry on tumour specimens, respectively [61]. A MSI or dMMR phenotype can be find in 1.7-46% or 2.4-57%, respectively [61]. As for any clinical suspicion of hereditary UTUC, those with a positive test should also undergo germline DNA sequencing and family counselling [52, 62-65] (Figure 3.1).

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



**These patients may benefit from MMR deficiency screening using PCR or IHC. Positive result should prompt subsequent testing for germline DNA sequencing mutations.*
MMR = mismatch repair; mismatch repair genes = MLH1, MSH2, MSH6, and PSM2; UTUC = upper urinary tract urothelial carcinoma.

Other germline mutations in MSH2, BRCA2, BRCA1 and BRIP1 have been shown to significantly increase the risk of developing UTUC in Chinese patients [66]. Differences in the exposure and susceptibility to carcinogens such as smoking may explain the differences in susceptibility to genetic predisposing mutations to go on to develop 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 previously mentioned. So far, two UTUC-specific polymorphisms have been reported [67]. Upper urinary tract UCs may also share some molecular pathways with BC [29]. However, familial clustering independent of smoking-related behaviours was only observed in BC and not UTUC patients in a large population-based case control study [68].

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 TURB, including prior to radical cystectomy, have been shown to have a higher risk for upper tract recurrence [69, 70].

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 [71, 72]. However, histological subtypes are present in approximately 25% of UTUCs [73, 74]. Pure squamous cell carcinoma of the urinary tract is often assumed to be associated with chronic inflammatory diseases and infections arising from urolithiasis [75, 76]. Urothelial carcinoma with divergent squamous differentiation (i.e., squamous subtype) is present in approximately 15% of cases [75]. Upper urinary tract UCs with different subtypes are high- grade and have a worse prognosis compared to pure UC [74, 77, 78]. Other subtypes are rare, inverted growths can be observed and can be difficult for staging [78-80].

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 [81].

3.4 Molecular background of UTUCs

A number of studies focussing on molecular classification have been able to demonstrate genetically distinct groups of UTUC by evaluating DNA, RNA and protein expression. The most common genomic alterations included FGFR3, chromatin remodelling genes (i.e., KMT2D and KDM6A), TP53/MDM2, and other typical tumour suppressors/oncogenes such as CDKN2A or RAS [82]. Low-grade tumours are enriched for activating FGFR3 mutations (> 90% tumours) and depleted of TP53/MDM2 mutations, whereas high-grade tumours often show mutations in TP53 signalling [83]. It has also been shown that UTUC has a T-cell depleted immune contexture and activated FGFR3 signalling [84]. Five different molecular variants with different gene expression, tumour location and outcome have been identified, but, as yet, it is unclear whether these variants will respond differently to treatment and therefore, these variants have limited use in daily practice [85].

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 DNA sequencing in patients with clinical suspicion of hereditary upper urinary tract urothelial carcinomas (UTUC).	Strong
Offer testing for mismatch repair (MMR) 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 [86], flat lesions (carcinoma *in situ* [CIS]), and invasive carcinoma in biopsies. Therefore, histological grade is often used for clinical decision making as it is strongly associated with pathological stage [87].

4.2 Tumour Node Metastasis staging

The Tumour, Node, Metastasis (TNM) classification is shown in Table 1 [88]. The regional lymph nodes (LNs) are the hilar and retroperitoneal nodes and, for the mid- and distal ureter, the pelvic nodes. Laterality does not affect N classification.

4.3 Tumour grade

In 2004 and 2022, the WHO published a new histological classification of UCs which provides a different patient stratification between individual categories compared to the older 1973 WHO classification [89-91]. These guidelines are still based on both the 1973 and 2004/2016 WHO classifications since most published data use the 1973 classification [86].

Table 1: TNM classification 2017 for upper tract urothelial cell carcinoma [88]

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]. Pre-operative symptoms at diagnosis are associated with a worse prognosis [92]. 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 [93]. 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) [94].

Rapid acquisition of thin sections allows high-resolution isotropic images 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 [95, 96]. The risk of thoracic metastases is extremely low in low-risk UTUC (see section 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 [97]. The sensitivity of MR urography is 75% after contrast injection for tumours < 2 cm [97]. Computed tomography urography is more sensitive and specific for the diagnosis and staging of UTUC compared to MR urography [98].

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/computed tomography (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) [99]. These results warrant further validation and comparison with MR and CT. FDG-PET can also be used to assess (nodal and distant) metastases in patients unfit for iodinated contrast media due to renal impairment and/or allergy.

5.3 Cystoscopy

Urethrocystoscopy is an integral part of the UTUC work-up to rule out concomitant BC [8, 20].

5.4 Cytology and urinary markers

Voided cytology may indicate high-grade UTUC when bladder cystoscopy is normal, and in the absence of CIS in the bladder and prostatic urethra [1, 100]. Voided urine cytology is less sensitive for UTUC than selectively obtained cytology from the affected upper tract [101]. In a recent study, barbotage cytology detected up to 91% of cancers [102]. Barbotage cytology taken from the renal cavities and ureteral lumina is preferred before application of a contrast agent for retrograde ureteropyelography as it may cause deterioration of cytological specimens [100, 102]. Retrograde ureteropyelography remains an option to detect UTUC [87, 103, 104]. The sensitivity of fluorescence *in situ* hybridisation (FISH) for molecular abnormalities characteristic of UTUC is approximately 72–84% [105, 106]. In a systematic review, including 25 studies on cytology and urinary markers, cytology and FISH were most commonly used [107]. FISH had comparable specificity (80-100%) and a higher sensitivity (35-86%) compared to cytology (11-71%). However, considering the wide ranges in sensitivity and specificity for both cytology and FISH, the authors concluded that these tests were suboptimal to rule out UTUC. A prospective study in 79 patients with suspicion of UTUC using upper tract urine collected just before URS, reported sensitivities for Xpert Bladder, FISH, Bladder Epicheck and cytology of 100%, 87%, 64% and 42% , respectively. Specificities were 4%, 82%, 79% and 94%, respectively [108]. FISH, Bladder Epicheck and cytology could be helpful as an ancillary tool to detect UTUC; however, further confirmation in well-designed prospective comparative trials is needed.

5.5 Diagnostic ureteroscopy

Flexible ureteroscopy (URS) is used if it is necessary to confirm the diagnosis of UTUC by visualising the ureter, renal pelvis and collecting system and to perform a biopsy of suspicious lesions. It is also essential for meticulous tumour mapping before considering kidney-sparing options for UTUC. Presence, appearance, multifocality and size of the tumour can be estimated during URS. In addition, ureteroscopic biopsies can determine tumour grade in over 90% of cases with a low false-negative rate, regardless of sample size [109]. However, undergrading and understaging leading to inaccurate risk stratification occurs with ureteroscopic diagnostic biopsy compared to nephroureterectomy specimens [87, 110, 111].

Ureteroscopy also facilitates selective ureteral sampling for cytology [104, 112, 113]. Stage assessment using ureteroscopic biopsy can be inaccurate, hence, combining ureteroscopic biopsy grade, imaging findings, and urinary cytology may help in the decision-making process between radical nephroureterectomy (RNU) and kidney-sparing approach [113, 114]. In a meta-analysis comparing URS vs. no URS prior to RNU, 8 out of 12 studies found an increased risk for intravesical recurrence in those undergoing URS [115]. Performing a biopsy at time of URS was also identified as a risk factor for intravesical recurrence [115]. A second systematic review of 16 studies showed that URS alone was not significantly related to intravesical recurrence; whereas, URS with a biopsy significantly increased the risk for subsequent intravesical recurrence albeit without an impact on extra urinary tract recurrences and overall survival [116].

Technical developments in flexible ureteroscopes and the use of novel imaging techniques may improve visualisation and diagnosis of flat lesions [117]. Narrow-band imaging is a promising technique, but results are preliminary [118]. 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 [119, 120].

5.6 Molecular Testing

FGFR 2/3 alterations should be tested for by NGS (see section 7.3.2.2.3) in the metastatic setting preferably from an invasive part of the tumour or metastatic site [121, 122].

5.7 Summary of evidence and recommendations for the diagnosis of UTUC

Summary of evidence	LE
The diagnosis and staging of UTUC is best achieved with computed tomography urography and URS.	2a
Selective urinary cytology has high sensitivity in high-grade tumours, including carcinoma *in situ*.	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 MRI 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.	Weak
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 FGFR 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 [113, 123-125]. Upper urinary tract UCs that invade the muscle have a poor prognosis. In a large Dutch series of UTUC, 5-year CSS was 86% for non- muscle-invasive tumours, 70% for muscle-invasive organ-confined tumours and 44% for locally-advanced tumours [18]. A contemporary SEER analysis of RNUs for high-risk disease showed that 5-year CSS was 86% for T1N0, 77% for T2N0, 63% for T3N0 and 39% for T4N0/T any N1–2 [126].

6.1.1 Pathological and histological grade

Tumour grading reflects tumour aggressiveness and could serve as a surrogate predictor of disease progression. A higher tumour grade has been shown to be associated with high rates of disease recurrence and worse cancer-specific survival following initial RNU [13, 127]. In fact, histological grade is one of the most important surrogate markers for pathological stage 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 radical nephroureterectomy [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 [74]. Most studied subtypes are micropapillary [77], squamous [128] and sarcomatoid [77], all of which are consistently associated with locally-advanced disease and worse outcomes [75]. 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 CT

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 [94]. A meta-analysis reported that CT urography has a sensitivity of 92% and a specificity of 95% for identifying muscle-invasive disease [94]. Moreover, another study demonstrated that CT can accurately predict pathological stage, particularly when identifying peripelvic fat invasion and non-organ confined tumours (NOCT), which are critical indicators of

advanced UTUC [129]. While biopsies may sometimes under-stage UTUC due to limited sample size, CT imaging offers a non-invasive and comprehensive assessment of tumor invasion, especially in cases of large or deeply invasive lesions [129]. For local staging, CT urography can also provide additional information on local invasion into renal parenchyma, renal pelvis and peri-ureteric tissue [130]. After adjusting for tumour size and hydronephrosis, local invasion on CT remains a significant risk factor for non-organ-confined disease [130]. These findings indicate that CT urography is a valuable modality in the pre-operative assessment of UTUC, guiding appropriate treatment strategies based on tumour stage, particularly NOCT. 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 [131-135]. Patients with multifocal tumours are more likely to harbour advanced tumour stage and a worse prognosis despite treatment with RNU [131-135]. 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 [134], while others focus on tumour location (i.e., both renal pelvis and ureter) [131-133, 135, 136]. Therefore, tumour multifocality should not be used alone for risk stratification.

6.1.5 ***Hydroureteronephrosis***

Hydroureteronephrosis has been linked to advanced disease and poor prognosis in patients treated with RNU [95, 137, 138]. A meta-analysis of 22 studies involving 7,542 patients found pre-operative hydroureteronephrosis to be significantly associated with ureteral tumour location, advanced tumour stage, and lymph node metastasis [139]. In addition, preoperative hydroureteronephrosis was independently associated with worse overall, cancer-specific, and disease-free survival [139].

However, 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 tumors 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).

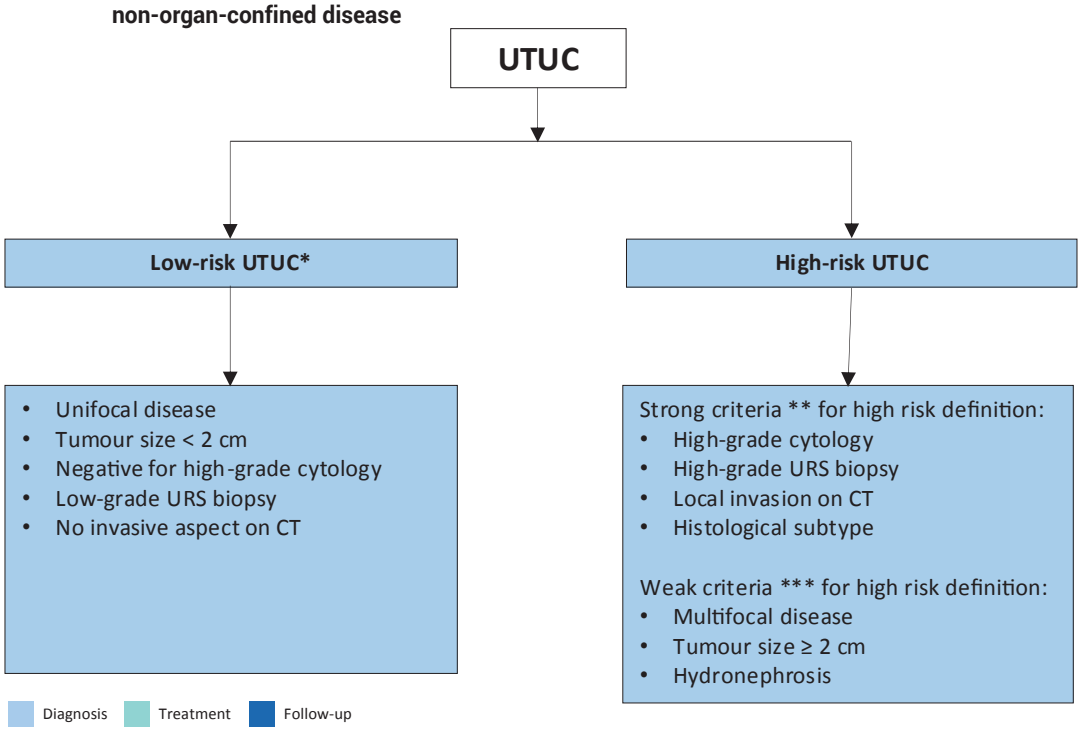
6.1.6 ***Tumour Size***

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 [140]. A meta-analysis of 32,292 patients confirmed that larger tumours are significantly associated with worse overall, cancer-specific, and disease-free survival, as well as intravesical recurrence [140]. In renal pelvis UTUC, where the median tumour size ranges from 3.5 to 4.0 cm, each 1 cm increase in tumour size elevates the risk of harboring muscle-invasive disease at RNU by 1.25-fold [141]. A multi-institutional study with 932 patients suggested that a 2 cm tumour size serves as the optimal threshold for identifying high-risk patients (> pT2 UTUC) [142]. 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. It should be considered as a continuous variable associated with stage but is insufficient by itself for precise risk stratification.

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

The factors to consider for risk stratification as well as the weight given to each factor are presented in Figure 6.1. 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 UTUC according to the risk of progression to a > pT2/ non-organ-confined disease



** All these factors need to be present.*
***Any of these factors need to be present.*
****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 [27]. Three categories of predictors for increased risk of bladder recurrence were proposed:

1. Patient-specific factors such as male gender, previous BC, smoking and pre-operative chronic kidney disease.
2. Tumour-specific factors such as positive pre-operative urinary cytology, tumour grade, ureteral location, multifocality, tumour diameter, invasive pT stage, and necrosis [143, 144].
3. 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 [145-147].

6.3 Summary of evidence and recommendation for the prognosis of UTUC

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 [148]. This is supported by population-based data reporting increased use of invasive diagnostic modalities in hospitals with lower case-load [147].

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 [149]. In low-risk cancers, kidney-sparing surgery is the preferred approach as survival is similar to that after RNU [149, 150]. This option should therefore be discussed in all low-risk cases, irrespective of the status of the contralateral kidney, in a shared-decision making process with the patient. Recommendations for kidney-sparing management of UTUC are listed in Section 7.1.7.

7.1.2 ***Ureteroscopy***

Endoscopic ablation should be considered in patients with low-risk cancer [151, 152]. A flexible ureteroscope is useful in the management of pelvicalyceal tumours [153]. The patient should be informed of the need and be willing and able to comply with an early second-look URS [154] and stringent surveillance; complete tumour resection or destruction is necessary [154]. Nevertheless, a risk of disease progression remains with endoscopic management due to the suboptimal performance of imaging and biopsy for risk stratification and tumour biology [155]. A systematic review reported comparable survival outcomes after endoscopic treatment to RNU at the cost of higher local recurrence rates and repeated interventions, but also with some uncertainties about long-term renal preservation after endoscopic treatment [156].

Tumour ablation of UTUC during URS is typically performed using holmium and/or thulium lasers, which allow tumour resection while minimising damage. The procedure involves direct visual identification of the tumour, followed by laser vaporisation or excision, and is often followed by meticulous irrigation to ensure no residual tumour fragments remain.

Second-look URS after initial endoscopic treatment is recommended in the conservative management of UTUC 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 [154]. 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 [157]. 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 access***

Percutaneous management can be considered for low-risk UTUC in the renal pelvis [151, 158]. This may also be offered for low-risk tumours in the lower caliceal system that are inaccessible or difficult to manage by flexible URS. However, this approach is being used less due to the availability of improved endoscopic tools such as distal-tip deflection of recent ureteroscopes [152, 158]. Moreover, a risk of tumour seeding remains with percutaneous access [158].

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 [159, 160]. Segmental resection of the proximal two-thirds of ureter is associated with higher failure rates than for the distal ureter [161, 162]. Distal ureterectomy with ureteroneocystostomy for tumours in the distal ureter is reported with a low cumulative incidence of ipsilateral upper tract recurrence (0-18%) [163-165] compared to 25-85% after endourologic kidney sparing [156].

7.1.5 *Chemo-ablation*

A single-arm phase III trial including 71 patients with biopsy-proven low-grade UTUC measuring less than 15 mm showed that the use of mitomycin-containing reverse thermal gel (UGN-101) instillations (6 weekly induction) in a chemoablation setting via retrograde catheter to the renal pelvis and calyces was associated with a complete response rate in a total of 41 patients (58%) [166]. 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%) and nausea in 17 (24%), while 19/31 (61%) reported ureteric stenosis requiring treatment. Among patients with complete response, 29/41 (71%) received at least one maintenance instillation (median of 6), and 23/41 (56%) remained disease free at one year [166].

7.1.6 *Adjuvant instillations*

7.1.6.1 *Upper urinary tract*

The antegrade instillation of BCG or mitomycin C in the upper urinary tract via percutaneous nephrostomy after complete tumour eradication has been studied for CIS after kidney-sparing management [167, 168]. Retrograde instillation through a single-J open-ended ureteric stent is also used. Before both the antegrade and retrograde approach a nephro-ureterogram needs to rule out ureteric obstruction or leakage, asses that there is no infection and ensure a low-pressure system to avoid pyelovenous influx during instillation/perfusion. The reflux obtained from a double-J stent has been used but this approach is suboptimal because the drug often does not reach the renal pelvis [169-172].

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 [173]. 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 [174]. The authors report limited complications related to the instillations and confirm the need for a retrograde pyelography before instillations are commenced to exclude contrast extravasation.

7.1.6.2 *Bladder*

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

7.1.7 *Recommendations for kidney-sparing management of localised low-risk UTUC*

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 patients.	Strong
Perform second look ureteroscopy within eight weeks following initial endoscopic management.	Weak

7.2 Localised high-risk disease

7.2.1 *Radical nephroureterectomy*

7.2.1.1 *Surgical approach*

Although the open approach has long been standard [13], laparoscopic and robot-assisted RNU can both be used to treat high-risk UTUC, providing peri-operative benefits such as decreased risk of complication and shorter hospital stay [175-178]. In addition, equivalent oncological outcomes have been reported between the three procedures [175-177, 179-183], except for a higher risk of intravesical recurrence after robotic RNU [184]. It is noteworthy that, although laparoscopic RNU was historically purported to provide inferior oncological outcomes [185], with higher risk of retroperitoneal dissemination or trocar metastases [186, 187], in locally-advanced UTUC, this was not confirmed with the use of robotic RNU [184].

A meta-analysis of six retrospective comparative studies, showed that the use of a retroperitoneal vs. transperitoneal route at the time of laparoscopic RNU provides similar peri-operative and oncological outcomes, except for a longer operative time and shorter recovery time to bowel function [188]. Similarly, retroperitoneal robotic RNU is safe and feasible [189].

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

1. Perform *en bloc* removal of the kidney, ureter and bladder cuff.
2. 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.

7.2.1.2 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 [27, 161, 190-192]. Several techniques have been considered to simplify distal ureter resection, including the pluck technique, stripping, transurethral resection of the intramural ureter, and intussusception. None of these techniques have convincingly been shown to be equal to complete bladder cuff excision [28, 190].

7.2.1.3 Lymph node dissection

There is no high-level evidence to support the use of LND for upper tract tumours. However, template-based and completeness of LND may improve CSS and reduce the risk of local recurrence [193]. Even in clinically [194] and pathologically [195] node-negative patients, LND may improve survival. Given that the risk of LN metastasis decreases with lower tumour stage [196], LND is likely unnecessary in patients with Ta/T1 UTUC [197-200]. However, clinical tumour staging is inaccurate pre-operatively; therefore, a template-based LND should be offered to all high-risk patients who are scheduled for RNU, especially given the low risk of major post-operative complications [201]. The templates for LND vary according to primary tumour location [193, 202, 203] and their use is likely to have a greater impact on survival than the number of removed LNs [204].

7.2.2 ***Kidney-sparing surgery***

7.2.2.1 Distal ureterectomy

Distal ureterectomy, especially with adequate surgical margins based on frozen section analysis, followed by ureteroneocystostomy for high-risk UTUC located in the distal ureter only may be associated with similar oncological outcomes as RNU [149, 150, 205, 206]. This procedure can be performed with concomitant LND. However, given the low level of evidence, this approach should only be used in highly selected cases where the benefits may be greater than the potential risks.

Ureterorenoscopy or segmental ureterectomy

For patients with high-risk UTUC but harbouring low-grade disease without any infiltrative features at imaging, tumour size and multifocality as well as hydronephrosis cannot be systematically considered as an indication for RNU [207, 208]. Alternatively, the use of ureterorenoscopy with laser ablation or segmental ureterectomy can be proposed on a case-by-case basis if feasible.

7.2.2.2 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, 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- vs. low-risk UTUC with a direct impact on survival [149].

7.2.3 ***Peri-operative chemotherapy***

7.2.3.1 Neoadjuvant treatments

7.2.3.1.1 Chemotherapy

The primary advantage of neoadjuvant chemotherapy (NAC) is the ability to give cisplatin-based regimens when patients still have maximal renal function. Several retrospective studies evaluating the role of NAC have shown evidence of pathological downstaging and complete response rates at RNU [209-213] with a direct impact on OS [214]. Furthermore, NAC has been shown to result in lower disease recurrence- and mortality rates compared to RNU alone, without compromising the use of definitive surgical treatment with a potential OS benefit [212, 215-217].

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 complete response rate in high-grade and/or cT2-T4N0M0 UTUC [218, 219]. 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 survival benefit compared with RNU alone [220]. A further systematic review and meta-analysis of 14 trials, with 117 UTUC patients across 21 studies included 1,983 who received NAC. Of these 10% had pCR and 42% pathological downstaging but no survival outcome benefit was demonstrated [221]. However, it is important to note that the evidence in the meta-analysis is not conclusive, given the significant bias and heterogeneity of the available data and the lack of distinction between truly neoadjuvant and downstaging chemotherapy.

7.2.3.1.2 Immunotherapy

Only a small phase II study including 10 patients with high-risk UTUC evaluated the efficacy of pembrolizumab in the neoadjuvant setting [222]. However, no pathological response was observed and one treatment-related death was reported. Thus, there is currently no evidence to support the use of neoadjuvant immunotherapy for high-risk UTUC.

7.2.3.2 Adjuvant treatments

7.2.3.2.1 Bladder instillations

The rate of bladder recurrence after RNU for UTUC is 22–47% [190, 223]. Two prospective randomised trials [224, 225] and two meta-analyses [226, 227] have demonstrated that a single post-operative dose of intravesical chemotherapy (mitomycin C, pirarubicin) 2–10 days after surgery reduces the risk of bladder tumour recurrence within the first years post-RNU in patients without a history of BC. Prior to instillation, a cystogram can be considered if there is concern about drug extravasation. All studies showed a very low risk of adverse events. Intravesical chemotherapy has also been safely given at the time of RNU prior to bladder cuff opening, removing the need for a post- operative cystogram, but with low level data for efficacy [228].

Based on current evidence it is unlikely that additional instillations beyond one peri-operative instillation of chemotherapy further substantially reduce the risk of intravesical recurrence [229]. 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 [230].

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

7.2.3.2.2 Systemic Chemotherapy

The POUT phase III multicentre prospective RCT (n = 261) evaluating the benefit of four cycles of adjuvant gemcitabine-platinum combination chemotherapy initiated within 90 days after RNU vs. surveillance has reported a significant improvement in disease-free survival (DFS) in patients with pT2–pT4, N (any) or positive (pT any, N1–3) M0 UTUC (3 year DFS 71% vs. 50%; 5 year DFS 63% vs. 46%; HR: 0.54; CI: 0.36-0.79; 3 & 5 year MFS 19% improvement HR: 0.55 CI: 0.0.36-0.77) [231]. Patients were stratified to gemcitabine/cisplatin or gemcitabine/carboplatin chemotherapy based on GFR alone with benefit seen irrespective of chemotherapy type. There was a non-significant trend towards improved OS (12% at 3 years) but as the study had met its primary endpoint of 3-year DFS, it closed early, leaving it underpowered for the secondary endpoint of OS. Updated analysis showed 5-year DFS of 62% vs. 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% vs. 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 [232]. 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 [233, 234]. A review of perioperative predictors of decline in renal function after RNU showed 3-month GFR levels of around 50 mls/min [235]. With split dose and hydration cisplatin may be considered in patients with a GFR down to 45 mL/min. Table 2 outlines the eligibility criteria for platinum chemotherapy.

A potential nomogram to predict deterioration in post RNU renal function has been developed in 733 UTUC patients and validated in a retrospective cohort of 367 patients [236]. Multivariable predictors of post-operative eGFR decline included advanced age (OR: 0.18, 95% CI: 0.28-0.08), diabetes (OR: 2.38, 95% CI: 4.64 - 0.11), and hypertension (OR: 2.24, 95% CI: 4.16 - 0.32). Factors associated with favourable post-operative eGFR included larger tumour size (OR: 10.57, 95% CI: 7.4–13.74 for tumours > 5 cm vs. 2 cm) and pre-operative eGFR (OR: 0.44, 95% CI: 0.39 - 0.49). A composite nomogram predicted post-operative eGFR with good accuracy in both the discovery (80.5%) and validation (78.6%) cohorts. Limitations include exclusion of patients who received neoadjuvant chemotherapy.

In a retrospective study histological subtypes of UTUC exhibit different survival rates and adjuvant chemotherapy was only associated with an OS benefit in patients with pure UC [237]. 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 > 50–60 mL/min ***and*** Audiometric hearing loss grade < 2 ***and*** Peripheral neuropathy grade < 2 ***and*** Cardiac insufficiency NYHA class < III	ECOG PS 2 *or* GFR 30–60 mL/min ***or*** not fulfilling other cisplatin-eligibility criteria	Any of the following: • GFR < 30mL/min • ECOG PS > 2 • ECOG PS 2 *and* GFR < 60mL/min • Comorbidites > Grade 2

**** Carboplatin is not indicated for neoadjuvant treatment***

7.2.3.2.3 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 [238]. The patient population predominantly consisted of BC patients post-radical cystectomy, with an additional smaller cohort of patients with UTUC post-RNU (approx 25%). The median recurrence-free survival outside the urothelial tract in the entire intention-to-treat population was 22.9 months for nivolumab and 13.7 months for placebo. Treatment-related adverse events > 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. Nonetheless, 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. [239]. A further study of 702 patients with urothelial cancer treated with either radical cystectomy or RNU, and with persistent high-risk features were randomised to receive either adjuvant pembrolizumab or observation [240]. 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 [240].

A network meta-analysis suggests superior oncological benefit for adjuvant platinum-based chemotherapy over immune checkpoint inhibitors in patients treated with radical surgery for UTUC [241].

7.2.3.2.4 Radiotherapy

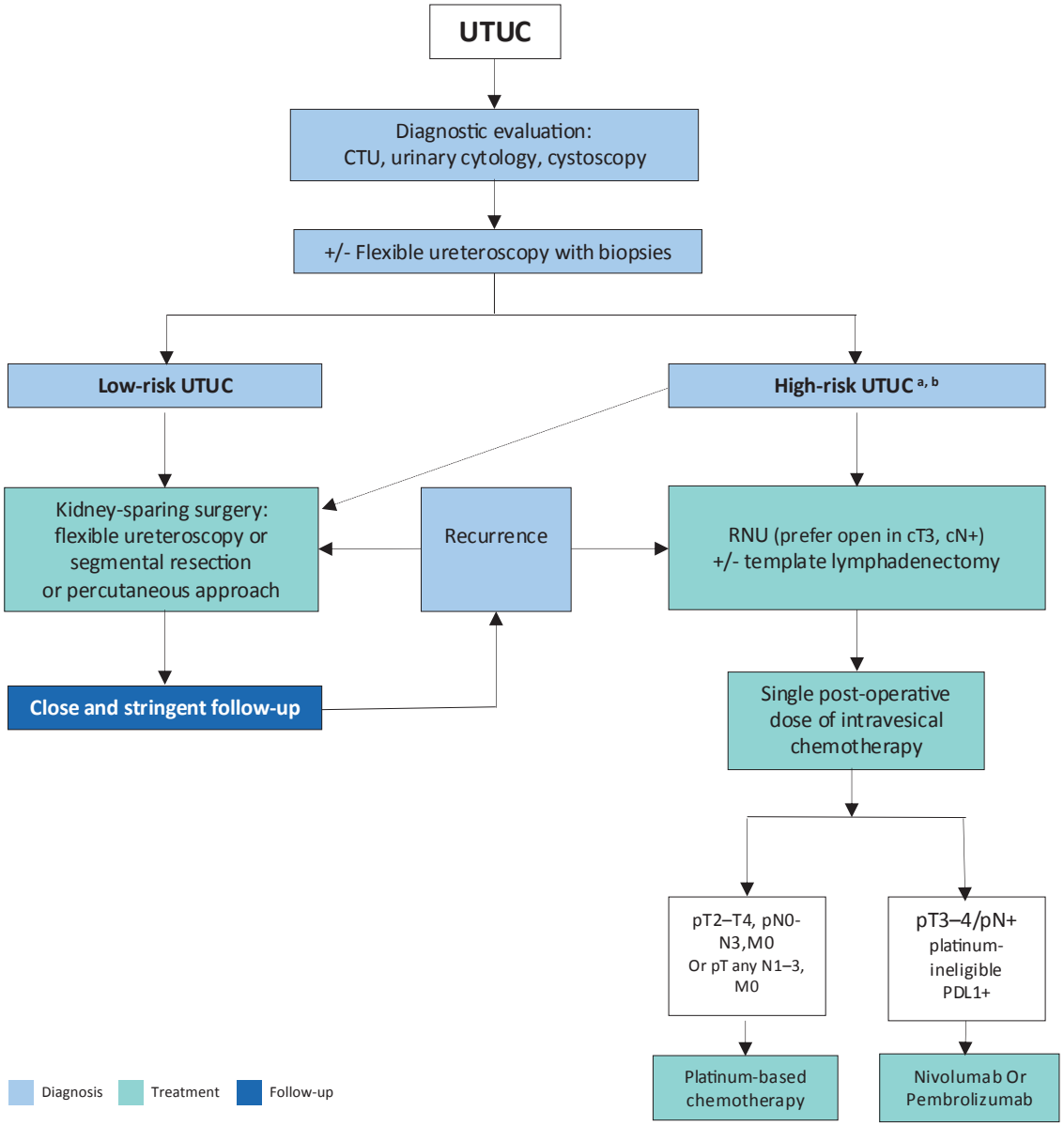
Adjuvant radiation therapy has been suggested to control loco-regional disease after surgical removal. The data remains controversial and insufficient for conclusions [242-245]. Moreover, its added value to chemotherapy remains questionable [244].

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

Summary of evidence	LE
Radical nephroureterectomy is the standard treatment for high-risk UTUC, regardless of tumour location.	2a
Open, laparoscopic and robotic approaches have similar oncological outcomes.	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
Post-operative platinum-based adjuvant chemotherapy improves disease-free survival.	1b
Single post-operative intravesical instillation of chemotherapy lowers the BC recurrence rate.	1b

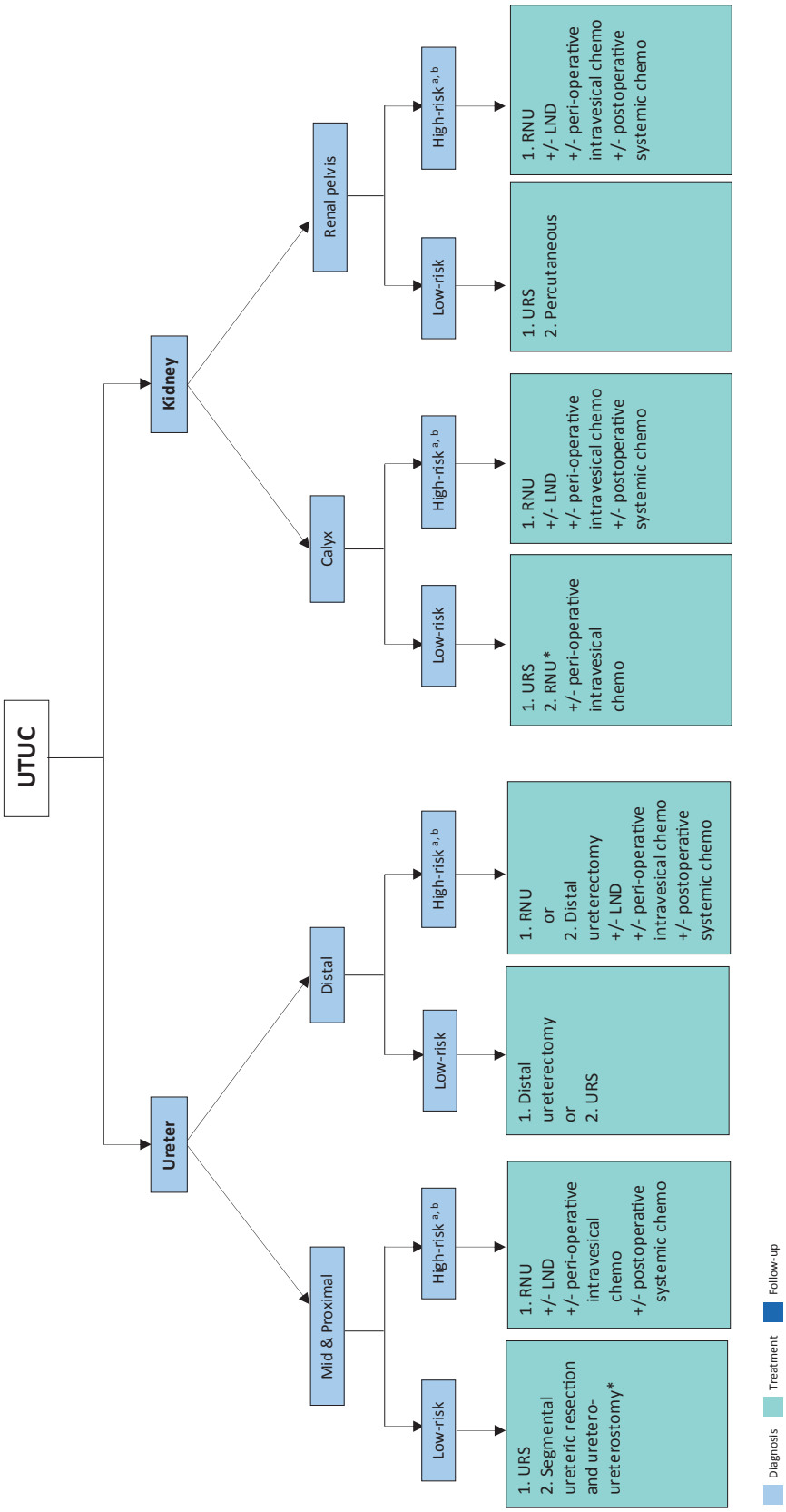
Recommendations	Strength rating
Discuss all patients with suspicion of upper tract urothelial carcinoma (UTUC) on imaging in a multidisciplinary team meeting.	Strong
Perform radical nephroureterectomy (RNU) in patients with high-risk non-metastatic UTUC.	Strong
Use open, laparoscopic or robotic approach 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 post-operative bladder instillation of chemotherapy to lower the intravesical recurrence rate in patients without a history of bladder cancer.	Strong
Discuss adjuvant nivolumab with 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 to 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 UTUC



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; 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.
**In case 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 loco-regional lymph node metastases***

Resectable cN+ patients should be offered induction platinum-based chemotherapy. RNU with template-based LND can be discussed in a multidisciplinary team and with patients responding to initial systemic therapy. In patients whose cancer progress, second-line treatment can be offered, similar to distant metastatic disease [246, 247]. Unresectable cN+ patients should be treated as distant metastatic patients [248].

7.3.2 ***Distant metastases***

7.3.2.1 Systemic treatments - First-line setting

7.3.2.1.1 Enfortumab vedotin + pembrolizumab combination therapy

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

This study showed significant improvement in both PFS (HR: 0.45 [0.38-0.54]) and OS (HR: 0.47 [0.38-0.58]) with RR of 68% (vs. 44%) and CR 29%. Overall survival benefit was seen across subgroups regardless of cisplatin eligibility. The most common grade 3 or above TRAE 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 pre-planned subgroup analysis showed benefit irrespective of tumour location [249].

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

7.3.2.1.2 Patients ineligible for EV+Pembro and fit for cisplatin-based combination chemotherapy

Upper tract UC and urothelial BC both respond to systemic platinum-based chemotherapy. Eligibility to 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 [250]. Therefore, cisplatin-containing combination chemotherapy is the standard treatment for advanced or metastatic UTUC ineligible for EV + Pembro [2]. A number of cisplatin-containing chemotherapy regimens have proven efficacy although gemcitabine and cisplatin are the most widely used. The use of cisplatin-based chemotherapy is widely considered in patients with eGFR > 45 mL/min [250].

The efficacy of immunotherapy using PD1 or PD-L1 inhibitors has been evaluated in the first-line setting for the treatment of cisplatin/carboplatin-fit patients with metastatic UC, including those with UTUC [251]. First-line immune checkpoint inhibitors or the combination of platinum-based chemotherapy with immune checkpoint inhibitors have not previously resulted in positive significant survival advantages and were thus not previously recommended [252-254]. These studies included both cisplatin and carboplatin combinations.

A phase III RCT in advanced/metastatic urothelial cancer has now shown an overall benefit from the addition of nivolumab to chemotherapy (gemcitabine-cisplatin). Median OS was improved (21.7 months vs. 18.9 months HR: 0.78 [0.63-0.96]) as well as median PFS (7.9 months vs. 7.6 months HR: 0.72 [0.59-0.88]). Objective RR were 57.6% compared with 43.1% for chemotherapy alone [255]. Although there is no sub-group analysis based on tumour position in this study, 12.6% of patients had UTUC.

7.3.2.1.3 Patients ineligible for Ev+Pembro 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 [256], irrespective of PDL-1 status. In a recent critical re-analysis of RCTs comparing OS after cisplatin vs. carboplatin-based regimens in advanced UC, cisplatin conferred a minor OS benefit compared to carboplatin [257].

7.3.2.1.4 Maintenance therapy after first-line platinum-based chemotherapy

Maintenance avelumab is recommended in patients with complete/partial response or stable disease after 4–6 cycles of platinum-based chemotherapy, given in the first line setting only. Data from a phase III RCT showed that the use of avelumab maintenance 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) [258, 259]. 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) [260].

7.3.2.1.5 Patients unfit for any combination therapy

Pembrolizumab or atezolizumab are alternative choices for patients who are PD-L1 positive and not eligible/fit for platinum-based chemotherapy. In a single-arm phase II trial (n = 370) of cisplatin-ineligible UC, pembrolizumab monotherapy was associated with an objective response rate of 26% in 69 metastatic UTUC patients [261]. 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 [262]. Median OS in the overall cohort was 15.9 months and treatment-related toxicity was in line with previous studies [253].

7.3.2.2 Systemic treatments - later line setting

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

7.3.2.2.1 Platinum based chemotherapy

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

7.3.2.2.2 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) [263]. 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 which relapsed after platinum-based chemotherapy; it failed to show a significant OS advantage of atezolizumab compared to second-line chemotherapy [264].

Other immunotherapies such as nivolumab [265], avelumab [266, 267] and durvalumab [268] have shown objective response rates ranging from 17.8% [268] to 19.6% [265] 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 [267].

The immunotherapy combination of nivolumab plus ipilimumab has shown significant anti-tumour activity with objective response rate up to 38% in a phase I/II multicentre trial including 78 patients with metastatic UC experiencing disease progression after platinum-based chemotherapy [269]. Although UTUC patients were included in this trial, no subgroup analysis was available. Other immunotherapy combinations may be effective in the second-line setting but data are currently limited [270].

7.3.2.2.3 Novel agents

Fibroblast growth factor receptors (FGFR) inhibition

Erdafitinib, a pan-FGFR tyrosine kinase inhibitor of FGFR1–4, was associated with a 40% radiological response rate according to the Response Evaluation Criteria in Solid Tumours (RECIST) in a phase II trial of 99 patients with locally-advanced or metastatic UC who progressed after first-line chemotherapy and harboured a FGFR DNA genomic alterations (FGFR2/3 fusions or FGFR3 mutations) [122]. 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 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 (vinfunine or docetaxel). Significant improvements in median OS, (4.3 months; HR: 0.64; CI: 0.47-0.88), PFS 2.9 months (58; CI: 0.44-0.78) and a 36% risk reduction in death were observed; 33.5% of patient in this study had UTUC [271]. As the rate of activating alterations of FGFR3 is higher in UTUC than in bladder cancer [272], a potentially greater impact of FGR3 targeting agents is anticipated. UTUC patients should be tested for FGFR alterations (FGFR2/3

mutations or FGFR3 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 (Table 5.7).

Antibody drug conjugates (ADC)

A phase II study enrolled 89 patients (of whom 43% 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 enfortumab vedotin. The objective radiological response rate (RECIST) was 52% of which 20% of patients achieved complete response [273]. In a phase III trial of enfortumab vedotin for the treatment of patients with locally-advanced or metastatic UC who had previously received platinum-containing chemotherapy and had disease progression during or after treatment with a PD-1 or PD-L1 inhibitor, enfortumab vedotin significantly prolonged survival as compared to standard chemotherapy (median OS 12.88 vs. 8.97 months) [274].

In an open-label phase II trial a total of 108 patients with metastatic UC who progressed after platinum-based chemotherapy and checkpoint inhibitors were treated with the antibody-drug conjugate sacituzumab govitecan. The objective radiological response rate was 27%, with median duration of response of 7.2 months, median PFS of 5.4 months and median OS of 10.9 months. However, the proportion of patients with UTUC was not mentioned in the publication [275].

A pre-planned subgroup analysis from the phase III RANGE trial assessed the impact on outcomes and safety of ramucirumab added to docetaxel after disease progression on both platinum-based chemotherapy and immune checkpoint inhibitors [276]. Median PFS was 3.15 months on ramucirumab/docetaxel vs. 2.73 months on placebo/docetaxel (HR: 0.786; 95% CI: 0.404–1.528, p = 0.4877). This trend for ramucirumab benefit occurred despite the ramucirumab arm having a higher percentage of patients with poorer prognosis. However, these findings need confirmation by further studies, as this analysis is limited by patient numbers and an imbalance in the treatment arms.

7.3.2.3 Surgery

7.3.2.3.1 Radical nephroureterectomy

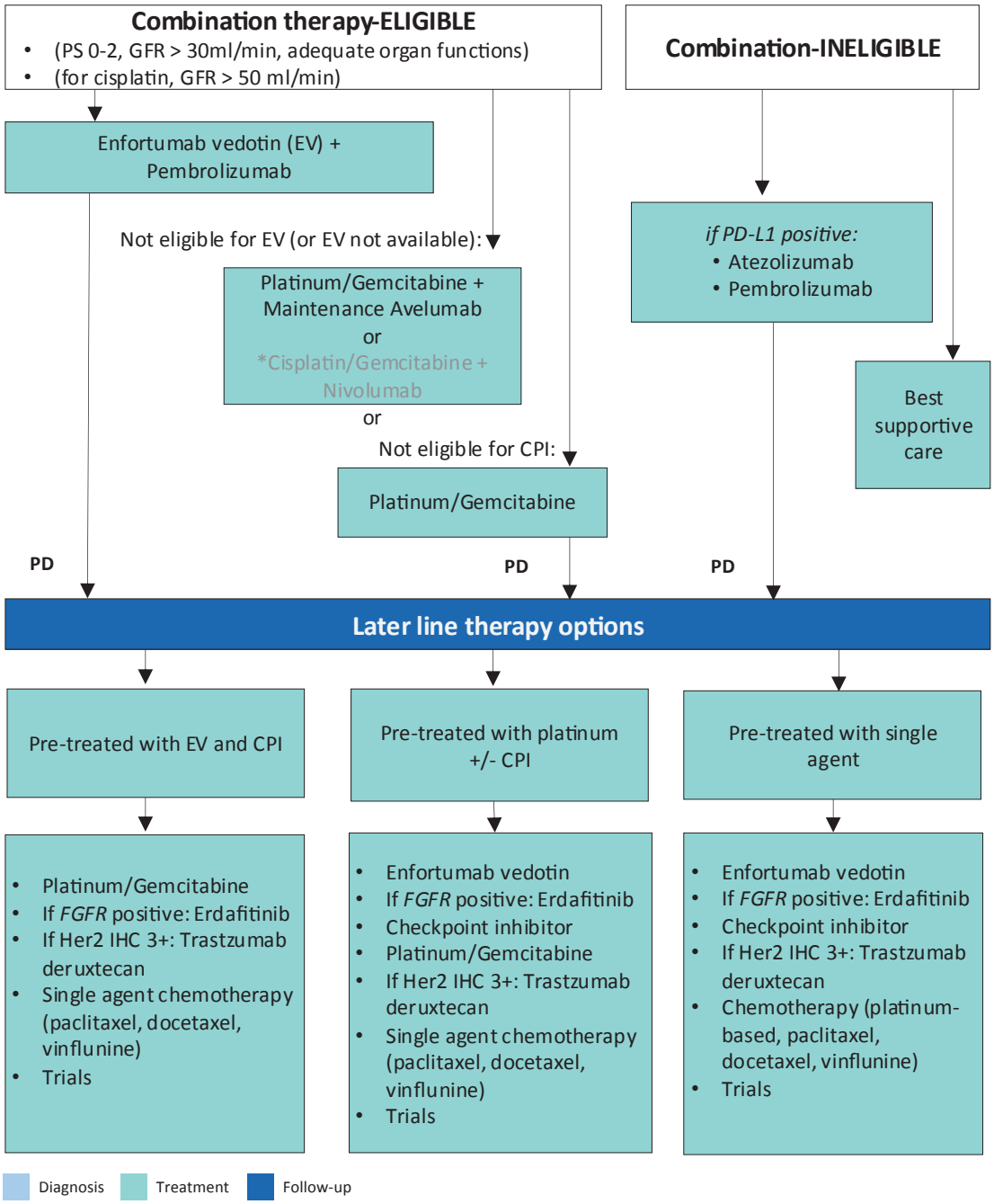
Data regarding RNU in the metastatic setting are lacking with mainly retrospective observational studies [277-279].

Although evidence remains very limited, RNU may be associated with CSS [278, 280, 281] and OS benefit in selected patients, especially those fit enough to receive cisplatin-based chemotherapy [277, 278]. It is noteworthy that these benefits may be limited to those patients with only one metastatic site [278]. 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 [22, 282].

7.3.2.3.2 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 [283-287]. 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.

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



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

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

Summary of evidence	LE
Enfortumab vedotin + Pembrolizumab offers an overall survival 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 Enfortumab + Pembrolizumab.	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 4 to 6 cycles of gemcitabine plus either cisplatin or carboplatin.	1b
PD-1 inhibitor pembrolizumab 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
PD-1 inhibitor nivolumab has been approved for patients that 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
PD-1 inhibitor pembrolizumab has been approved for patients with advanced or metastatic UC unfit for platinum-based first-line chemotherapy based on the results of a phase II trial but use of pembrolizumab is restricted to PD-L1 positive patients.	2a
PD-L1 inhibitor atezolizumab has been approved for patients with advanced or metastatic UC unfit for platinum-based first-line chemotherapy based on the results of a phase II trial, but use of atezolizumab is restricted to PD-L1 positive patients.	2a
Erdafitinib was associated with improved overall survival in platinum-refractory patients with locally-advanced or metastatic UC and FGFR DNA genomic alterations (FGFR2/3 mutations or FGFR3 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 nephroureterectomy can improve quality of life by controlling symptomatic disease.	3
RNU can confer a survival benefit in highly selected patients with metastatic UC e.g., after response to platinum-based combination chemotherapy with limited metastatic burden.	4

Recommendations	**Strength rating**
Offer Enfortumab vedotin in combination with pembrolizumab as first-line treatment to patients with advanced/metastatic disease.	Strong
First-line treatment for platinum-eligible patients who are unsuitable/ineligible for Enfortumab + Pembrolizumab	
Offer platinum combination chemotherapy to platinum-eligible patients.	Strong
Offer cisplatin-based chemotherapy with gemcitabine-cisplatin + 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 4 to 6 cycles of platinum-based combination chemotherapy.	Strong
First-line treatment in patients ineligible for any combination therapy	
Offer checkpoint inhibitors 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 checkpoint inhibitor (pembrolizumab) to patients with disease progression during or after platinum-based combination chemotherapy for metastatic disease who did not receive maintenance avelumab.	Strong
Offer enfortumab vedotin to patients previously treated with platinum-containing chemotherapy and who had disease progression during or after treatment with a PD-1 or PD-L1 inhibitor.	Strong

Offer erdafitinib as an alternative subsequent-line therapy to patients: • previously treated with platinum-containing chemotherapy; • who had disease progression during or after treatment with a PD-1 or PD-L1 inhibitor; • who harbour FGFR DNA genomic alterations (FGFR2/3 mutations or FGFR3 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 nephroureterectomy as a palliative treatment to symptomatic patients with resectable locally-advanced tumours.	Weak

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

8. FOLLOW-UP

The aims for follow-up after treatment for UTUC are to comply with patient rehabilitation needs, to detect recurrent or new primary tumours within the urothelium, and to detect regional and/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, a cystoscopy at three months post-operatively, a subsequent cystoscopy nine months later and yearly cystoscopies for five years [288]. 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 [289].

When RNU has been performed for high-risk tumours, stringent follow-up is mandatory to detect metachronous bladder tumours (probability increases over time [290]), local recurrence, and distant metastases. The risk of bladder recurrence is higher in patients with previous history of bladder cancer compared to those without, indicating the need for more intensive cystoscopy follow-up [291]. 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 thereafter may apply [291].

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 [154] 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 [292, 293].

In patients treated with kidney-sparing for high-risk tumours, the indication (imperative vs. non-imperative) affects the surveillance regimen by the consequences of recurrent disease. Still, the ipsilateral UUT requires careful and long-term follow-up due to the high risk of disease recurrence [153, 294, 295] and progression following RNU, even beyond five years [296].

Surveillance regimens are based on CT urography, cystoscopy and urinary cytology [290, 297]. There are, however, several unanswered questions related to the optimal follow-up of patients treated for both low-risk and high-risk UTUC, of which some are:

- The added value of new urinary markers compared to cytology in voided urine samples in high-risk patients [298].
- 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 [299].

- If adjuvant upper tract instillations have been administered after endourologic kidney-sparing management, will that allow for less vigorous follow-up?
- The role of ureteroscopies of the ipsilateral upper urinary tract during follow-up after endourologic kidney-sparing treatment vs. CT urography and voided urinary cytology.

Additionally, it is not known how patients with Lynch syndrome, without and with UTUC, should be screened or followed long-term given the inadequacy of surveillance based on urinalysis for nonvisible haematuria [300] and urine cytology [301], particularly in those individuals who are MSH2 mutation carriers [53] and those who already have developed a UTUC. Section 8.1 presents the summary of evidence and recommendations for follow-up of UTUC.

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

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

Recommendations	**Strength rating**
After radical nephroureterectomy	
Low-risk tumours	
Perform cystoscopy at three months. If negative, perform subsequent cystoscopy 9 months later and then yearly, for 5 years.	Weak
High-risk tumours	
In patients with previous history of NMIBC perform cystoscopy and voided urinary cytology at 3 months. If negative, repeat subsequent cystoscopy and cytology every 3 months for a period of 2 years, and every 6 months thereafter until 5 years, and then yearly.	Weak
In patients without previous history of NMIBC perform cystoscopy and voided urinary cytology at 3 months. If negative, repeat subsequent cystoscopy and cytology every 6 months for a period of 2 years, and every year thereafter until 5 years.	Weak
Perform computed tomography (CT) urography and chest CT every 6 months for 2 years, and then yearly.	Weak
After kidney-sparing management	
Low-risk tumours	
For bladder follow-up perform cystoscopy 3 and 6 months, and then yearly for 5 years.	Weak
For upper tract follow-up, after negative second look URS, perform cross sectional imaging urography at 3 and 6 months and then yearly for 5 years with or without URS*.	Weak
High-risk tumours	
In patients without previous history of NMIBC follow-up the same 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 3 and 6 months and then cross sectional imaging urography every 6 months for 2 years and then every year for 5 years, with or without URS*.	Weak

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

9. QUALITY INDICATORS FOR THE MANAGEMENT OF UTUC

Evidence based Quality Indicators (QIs) and Quaity Performance Indicators (QPIs) are designed to be surrogates of good practice and consequently, outcomes. They allow for the gap between efficacy and effectiveness to be narrowed, i.e., being able to bring research evidence and guideline recommendations into real world practice by improving compliance to them [302]. 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. They 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 post-operative single bladder instillation of chemotherapy and risk-adapted delivery of neoadjuvant or adjuvant systemic treatments [303].

In addition, the achievement of an RNU-specific pentafecta including negative surgical margins, complete bladder cuff removal, the absence of hematological or major complication and the absence of post-operative recurrence at twelve months has been shown to provide higher five year OS and CSS rates [304]. 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 post-operative recurrence at twelve months [305]. Finally, a hospital volume of > 6 patients per year treated with RNU was associated with improvement of short-term outcomes (30- and 90-day mortality) and overall long-term survival in a population-based study [306].

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11. CONFLICT OF INTEREST

All members of the Non-Muscle-Invasive Bladder Cancer Guidelines working panel have provided disclosure statements on all relationships that they have that might be perceived to be a potential source of a conflict of interest. This information is available on the European Association of Urology website: http://uroweb.org/guideline/upper-urinary-tract-urothelial-cell-carcinoma/.

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