EAU Guidelines on

Upper Urinary Tract Urothelial Carcinoma

A. Masson-Lecomte, P. Gontero (Chair), A. Birtle,
E.M. Compérat, J.L. Dominguez-Escrig, F. Liedberg,
P. Mariappan, A.H. Mostafid, B.W.G. van Rhijn,
T. Seisen, S.F. Shariat, E.N. Xylinas
Patient representative: R. Wood
Guidelines Associates: O. Capoun, B. Pradere,
B.P. Rai, F. Soria, V. Soukup
Guidelines Office: E.J. Smith, H. Ali

European Association of Urology

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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 consists of an international multidisciplinary group of clinicians, including urologists, uro-oncologists, a radiologist, a pathologist, and a patient representative. 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/.

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 2024 UTUC Guidelines presents an update of the 2023 version.

1.4.1 Summary of changes

For the 2024 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 the addition of:

- New text and guidelines updates in section 3.2.2 on the genetic risk factors and the implications of identifying lynch syndrome's related UTUCs, and in section 3.4 on the molecular background of UTUCs;
- new text updates in section 6.1.2.2 on tumour location, multifocality, size and hydronephrosis;
- updates in section 6.2 on the risk stratification for clinical decision making, both in text and evidence;
- key updates to the text, evidence and guidelines in section 7.3.2 on the management of distant metastases.

2. METHODS

2.1 Data identification

For the 2023 UTUC Guidelines, new and relevant evidence has been identified, collated, and appraised through a structured assessment of the literature. The search was restricted to articles published between May 4th 2022 and May 1st 2023. 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 333 unique records were identified, retrieved, and screened for relevance.

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

A detailed search strategy is available online: https://uroweb.org/guideline/upper-urinary-tract-urothelial-cell-carcinoma/?type=appendicespublications.

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 in the online: https://uroweb.org/eau-guidelines/methodology-policies.

2.2 Review

The UTUC Guidelines was subject to peer-reviewed 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 past or present 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 metastasis [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]. In 17% of cases, concurrent BC is present [20] whilst a prior history of BC is found in 41% of American men but in only 4% of Chinese men [21]. This, along with genetic and epigenetic factors, may explain why Asian patients present with more advanced and higher-grade disease compared to other ethnic groups [8].

Following treatment, recurrence in the bladder occurs in 29% of UTUC patients, depending on patient-, tumour- and treatment-specific characteristics [22] compared to a 2–5% recurrence rate in the contralateral upper tract [23].

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 [24].

Regarding UTUC occurring in patients with BC, of 82 patients treated with intravesical bacillus Calmette-Guérin (BCG) for high-risk BC who had regular upper tract imaging between years 1 and 3, 13% developed UTUC, all of which were asymptomatic [25], whilst in another series of 307 patients without routine upper tract imaging the incidence of UTUC after BC was 25% [26]. A multicentre cohort study (n = 402) with a 50 month follow-up demonstrated a UTUC incidence of 7.5% in NMIBC patients receiving BCG with predictors being intravesical recurrence and non-papillary tumour at transurethral resection of the bladder (TURB) [27]. Following radical cystectomy for MIBC, 3–5% of patients develop a metachronous UTUC [28, 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]. Published evidence in support of a causative role for these factors is not strong, with the exception of smoking and aristolochic acid. Tobacco exposure increases the relative risk of developing UTUC by 2.5 to 7.0 fold [31-33]. A large population-based study assessing familial clustering in relatives of UC patients, including 229,251 relatives of case subjects and 1,197,552 relatives of matched control subjects, has demonstrated genetic or environmental roots independent of smoking-related behaviours. With more than 9% of the cohort being UTUC patients, clustering was not seen for UTUC. This suggests that the familial clustering of UC is specific to the lower urinary tract (i.e., BC) [34].

Aristolochic acid, a nitrophenanthrene carboxylic acid produced by aristolochia plants, which are used worldwide for different health-related issues, especially in China and Taiwan [35], exerts negative effects on the urinary system. Aristolochic acid irreversibly injures renal proximal tubules resulting in chronic tubulointerstitial disease, while the mutagenic properties of this carcinogen can lead to UTUC [35-37]. Aristolochic acid has been linked to BC, renal cell carcinoma, hepatocellular carcinoma, and intrahepatic cholangiocarcinoma [38]. Two routes of exposure to aristolochic acid are known: (i) environmental contamination of agricultural products by aristolochia plants, as reported for Balkan endemic nephropathy [39]; and (ii) ingestion of aristolochia-based herbal remedies [40, 41]. Following bioactivation, aristolochic acid reacts with genomic DNA to form aristolactam-deoxyadenosine adducts [42]; these lesions persist for decades in target tissues, serving as robust biomarkers of exposure [43]. These adducts generate a unique mutational spectrum, characterised by A>T transversions located predominately on the non-transcribed strand of DNA [38, 44]. However, it is estimated that less than 10% of individuals exposed to aristolochic acid develop UTUC [37].

Two retrospective series demonstrated that aristolochic acid-associated UTUC is more common in females [45, 46]. However, females with aristolochic acid UTUC have a better prognosis than their male counterparts. Consumption of arsenic in drinking water and aristolochia-based herbal remedies together appears to have an additive carcinogenic effect [47]. In Taiwan and Chile, the presence of arsenic in drinking water has been tentatively linked to UTUC [48, 49].

In addition, alcohol consumption may be associated with development of UTUC. A large case-control study (1,569 cases and 506,797 controls) has evidenced a significantly higher risk of UTUC in ever-drinkers compared to never-drinkers (OR: 1.23; 95% CI: 1.08–1.40, p = 0.001). Compared to never-drinkers, the risk threshold for UTUC was > 15 g of alcohol/day. A dose-response 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 UTUCs 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 9% of patients with UTUC compared to 1% of patients with BC [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.

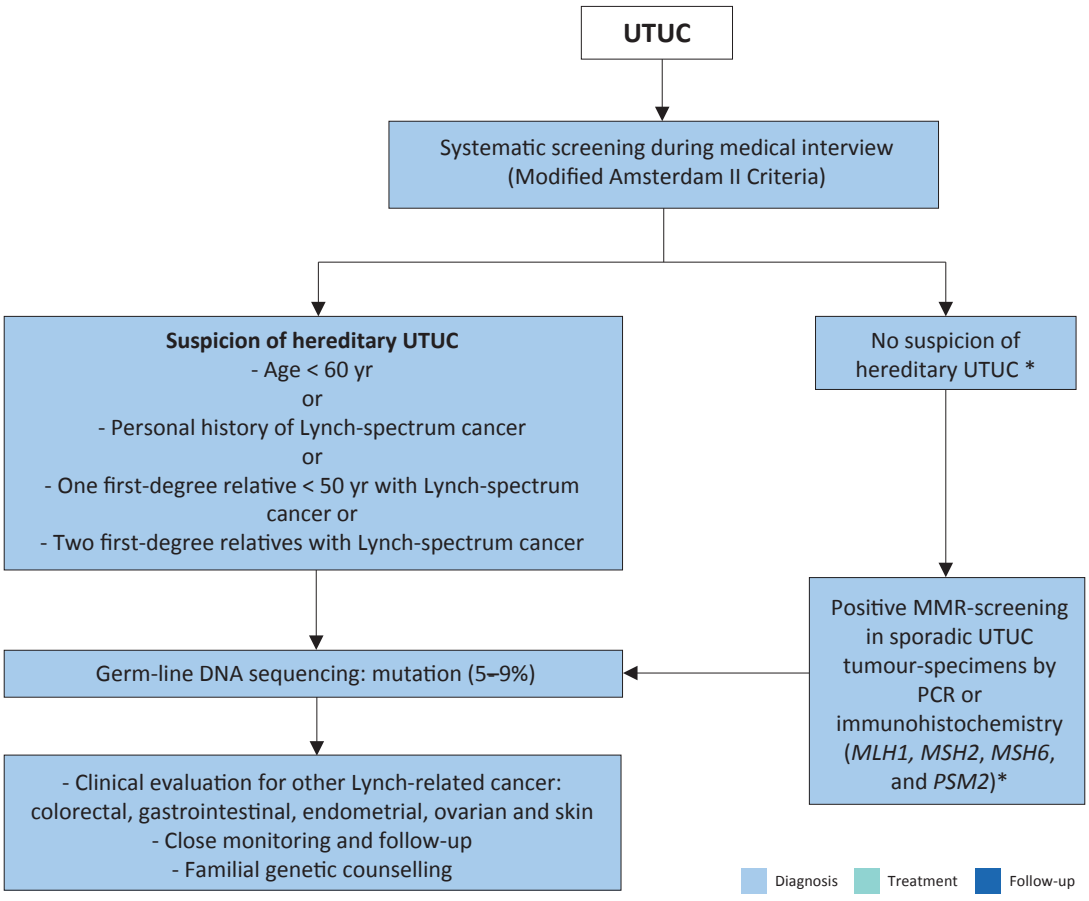
From a clinical perspective, although the PREMM5 model has been developed to estimate the cumulative probability of an individual to carry a germline mutation related to the Lynch syndrome [54], the Amsterdam II criteria remains predominantly used to identify families that are at increased risk of Lynch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

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, respectively. As for any clinical suspicion of hereditary UTUC, those with positive test should also undergo germline DNA sequencing and family counselling [52, 61-64] (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 has been shown to significantly increase the risk of developing UTUC in Chinese patients [65]. Differences in the exposure and susceptibility to carcinogens such as smoking may explain the differences in susceptibility to genetic predisposing mutations to overt disease. Some genetic polymorphisms are associated with an increased risk of cancer or faster disease progression that introduces variability in the inter-individual susceptibility to the risk factors previously mentioned. Upper urinary tract UCs may also share some risk factors and described molecular pathways with bladder UC [24]. So far, two UTUC-specific polymorphisms have been reported [66].

3.2.3 History of bladder cancer

A history of BC is associated with a higher risk of developing UTUCs (see Section 3.1). Patients requiring ureteral stenting at the time of TURB, including prior to radical cystectomy, have been shown to have a higher risk for upper tract recurrence [67, 68].

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 [69, 70]. However, histological subtypes are present in approximately 25% of UTUCs [71, 72]. Pure squamous cell carcinoma of the urinary tract is often assumed to be associated with chronic inflammatory diseases and infections arising from urolithiasis [73, 74]. Urothelial carcinoma with divergent squamous differentiation (i.e., squamous subtype) is present in approximately 15% of cases [73]. Keratinising squamous metaplasia of urothelium is a risk factor for squamous cell cancers and therefore mandates surveillance. Upper urinary tract UCs with different subtypes are high- grade and have a worse prognosis compared to pure UC [72, 75, 76]. Other subtypes, although rare, include sarcomatoid with inverted growth also being is frequent in the UUT [76, 77].

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 [78].

3.4 Molecular background of UTUCs

A number of studies focusing 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 [79]. 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 [80]. It has also been shown that UTUC has a T-cell depleted immune contexture and activated FGFR3 signalling [81]. Five different molecular subtypes with different gene expression, tumour location and outcome have been identified, but, as yet, it is unclear whether these subtypes will respond differently to treatment and therefore, these subtypes have limited use in daily practice [82].

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 UTUC.	Weak
Offer testing for 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 [83], 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 [84].

4.2 Tumour Node Metastasis staging

The tumour, node, metastasis (TNM) classification is shown in Table 1 [85]. The regional lymph nodes (LNs) are the hilar and retroperitoneal nodes and, for the mid- and distal ureter, the pelvic nodes. Laterality does not affect N classification.

4.3 Tumour grade

In 2004 and 2016, the WHO and the International Society of Urological Pathology published a new histological classification of UCs which provides a different patient stratification between individual categories compared to the older 1973 WHO classification [86, 87]. In 2022, an update of the 2004/2016 WHO grading classification was published without major changes [88]. These guidelines are still based on both the 1973 and 2004/2016 WHO classifications since most published data use the 1973 classification [83].

Table 1: TNM classification 2017 for upper tract urothelial cell carcinoma [85]

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

TNM = Tumour, Node, Metastasis (classification).

5. DIAGNOSIS

5.1 Symptoms

The diagnosis of UTUC may be incidental or symptom related. Flank pain, due to clot or tumour tissue obstruction can occur in 20–32% of cases [11]. 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]. Symptoms at diagnosis are associated with indicate a worse prognosis [89].

5.2 Imaging

*5.2.1 **Computed tomography***

Computed tomography (CT) urography has the highest diagnostic accuracy of the available imaging techniques [90]. 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) [91].

Rapid acquisition of thin sections allows high-resolution isotropic images that can be viewed in multiple planes to assist with diagnosis without loss of resolution. Epithelial "flat lesions" without mass effect or urothelial thickening are generally not visible with CT.

The presence of enlarged LNs on CT is highly predictive of metastases in UTUC [92, 93].

*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 [94]. The sensitivity of MR urography is 75% after contrast injection for tumours < 2 cm [94]. Computed tomography urography is more sensitive and specific for the diagnosis and staging of UTUC compared to MR urography [95].

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

A retrospective multicentre publication on the use of 18F-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 [96]. 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 or allergy.

5.3 Cystoscopy

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

5.4 Cytology and urinary markers

Abnormal cytology may indicate high-grade UTUC when bladder cystoscopy is normal, and in the absence of CIS in the bladder and prostatic urethra [1, 97]. Voided urine cytology is less sensitive for UTUC than selectively obtained cytology from the affected upper tract [98]. In a recent study, barbotage cytology detected up to 91% of cancers [99]. 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 [97, 99]. Retrograde ureteropyelography remains an option to detect UTUCs [84, 100, 101]. The sensitivity of fluorescence *in situ* hybridisation (FISH) for molecular abnormalities characteristic of UTUCs is approximately 72–84% [102, 103]. In a systematic review, including 25 studies on cytology and urinary markers, cytology and FISH were most commonly used [104]. 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 test were suboptimal to rule out cancer/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 [105]. 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 when necessary to confirm the diagnosis of UTUC by visualising the ureter, renal pelvis and collecting system and perform a biopsy of suspicious lesions. It is also essential for meticulous tumour mapping before considering kidney-sparing options for UTUC. Presence, appearance, multifocality and size of the tumour can be determined using URS. In addition, ureteroscopic biopsies can determine tumour

grade in more than 90% of cases with a low false-negative rate, regardless of sample size [106]. However, undergrading occurs with ureteroscopic diagnostic biopsy compared to nephroureterectomy specimens [107], making second-look URS necessary, as part of follow-up if kidney-sparing treatment is chosen [84, 108, 109] .

Ureteroscopy also facilitates selective ureteral sampling for cytology [101, 110, 111]. 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 therapy [111, 112]. 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 [113]. Performing a biopsy at URS was also identified as a risk factor for intravesical recurrence [113]. 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 overall survival and non-urothelial recurrence [114]. This underlines the need for a study evaluating whether an immediate intravesical instillation of chemotherapy in patients who underwent URS plus biopsy, or laser treatment, for UTUC can lower the intravesical recurrence rate after RNU (see section 7.2.4.2).

Technical developments in flexible ureteroscopes and the use of novel imaging techniques may improve visualisation and diagnosis of flat lesions [115]. Narrow-band imaging is a promising technique, but results are preliminary [116]. 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 [117, 118].

5.6 Summary of evidence and recommendations for the diagnosis of UTUC

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

Recommendations	Strength rating
Perform a urethrocystoscopy to rule out bladder tumour.	Strong
Perform chest, abdominal and pelvis with computed tomography (CT) urography for diagnosis and staging.	Strong
Use diagnostic ureteroscopy (URS) if imaging and voided urine cytology are not sufficient for the diagnosis and/or risk-stratification of patients suspected to have UTUC.	Strong
Magnetic resonance urography or ^{18}F-Fluorodeoxglucose positron emission tomography/CT may be used when CT is contra-indicated.	Weak

6. PROGNOSIS

6.1 Prognostic factors

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

*6.1.1 **Patient-related factors***

6.1.1.1 Age and gender

Older age at the time of RNU is independently associated with decreased cancer-specific survival (CSS) [119, 120]. Gender has no impact on prognosis of UTUC [121].

6.1.1.2 Ethnicity

A multicentre study of international patients from various academic centres did not show any difference in outcomes between races [122]. In contrast, U.S. population-based studies have indicated that African-American patients have worse outcomes than other ethnicities. The cause of this difference is unclear, possibly being related to access to care and/or biological patterns. Another study has demonstrated differences between Chinese and American patients at presentation in terms of risk factors, disease characteristics and predictors of adverse oncologic outcomes [21].

6.1.1.3 Genetic pre-disposition

Patients who test positive for Lynch syndrome, are significantly younger and exhibit a higher prevalence of UTUC with for ureteral location [123]. No impact on prognosis has been shown to date.

6.1.1.4 Tobacco consumption

Being a smoker at diagnosis increases the risk for disease recurrence, mortality [124, 125] and intravesical recurrence after RNU [126]. Smoking cessation over ten years improves outcomes to the level of non-smokers [125, 127].

6.1.1.5 Surgical delay

A delay between diagnosis of an invasive tumour and its removal may increase the risk of disease progression. Once a decision regarding RNU has been made, the procedure should be carried out within twelve weeks, whereas a treatment delay below four weeks has been suggested for the subgroup of patients with ureteral UTUC [128-132].

6.1.1.6 Other factors

High comorbidity and performance indices scores (e.g. American Society of Anesthesiologists [ASA], performance status [PS], and Charlson Comorbidity Index) are also associated with worse survival outcomes across disease stages [133-136].

A higher ASA score confers worse CSS after RNU [137], as does poor PS [138]. Obesity and higher body mass index adversely affect cancer-specific outcomes in patients treated with RNU [139], with potential differences between races [140]. Several blood-based biomarkers have been associated with locally-advanced disease and cancer-specific mortality such as high pre-treatment-derived neutrophil- lymphocyte ratio [141-144], low albumin [143-145], high C-reactive protein [143] or modified Glasgow score [146], high De Ritis ratio (aspartate transaminase/alanine transaminase) [147], altered renal function [143, 148] and high fibrinogen [143, 148].

*6.1.2 **Tumour-related factors***

6.1.2.1 Tumour stage and grade

The main prognostic factors are tumour stage and grade [111, 120, 149, 150]. 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 N1–3 [151]. pT3 sub staging (pT3a vs. pT3b) might be relevant [152]; however, high quality validation is lacking.

6.1.2.2 Tumour location, multifocality, size and hydronephrosis

6.1.2.2.1 Multifocality

Approximately 7-42% of UTUC patients have been reported to have multifocal tumours [153-157]. Patients with multifocal tumours are more likely to harbour advanced tumour stage and a worse prognosis despite treatment with RNU [153-157]. However, multifocal tumours can also have a good prognosis and be present in the setting of otherwise low-risk UTUC.

It is important to note that the definition of multifocality varies among studies. Some studies consider the number of lesions [156], while others focus on tumour location (i.e., both renal pelvis and ureter) [153-155, 157].

Taken together, tumour multifocality alone is insufficient for risk stratification, and a combination of factors is needed to determine whether kidney-sparing surgery is a safe option. Patients should be categorised as high-risk UTUC not only when tumour multifocality is present but when it is accompanied by high risk factors (see Figure 6.1).

6.1.2.2.2 Hydroureteronephrosis

Hydroureteronephrosis has been linked to advanced disease and poor prognosis in patients treated with RNU [92, 158, 159]. A recent 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 [160]. In addition, pre-operative hydroureteronephrosis was independently associated with worse overall, cancer-specific, and disease-free survival, but not intravesical recurrence [160].

It is important to note that some low-risk UTUC patients may exhibit hydroureteronephrosis with for example a pTa low-grade tumour obstructing the ureter. Taken together, just like tumour multifocality, the presence of hydroureteronephrosis alone is insufficient for risk stratification, and a combination of factors is needed to determine whether kidney-sparing surgery is a safe option. Patients should be categorised as high-risk UTUC not only when pre-operative hydroureteronephrosis is present but if it is accompanied by other high risk factors (see Figure 6.1).

6.1.2.2.3 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 [161]. A recent 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 [161]. 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 harbouring muscle-invasive disease at RNU by 1.25-fold [162]. A recent 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) [163]. However, measuring tumour size lacks standardisation, leading to inter-assessor variability.

Taken together, just like tumour multifocality and hydroureteronephrosis, tumour size alone is insufficient for risk stratification, and a combination of factors is needed to determine whether kidney-sparing surgery is a safe option. Therefore, similar to tumour multifocality and hydroureteronephrosis, tumour size alone should not dictate therapeutic decisions. Patients should be categorised as high-risk UTUC not only when tumour size exceeds 2 cm but if it is accompanied by other high risk factors (see Figure 6.1).

6.1.2.3 Pathological subtypes

Pathological subtypes are associated with worse CSS and overall survival (OS) [72]. Most studied subtypes are micropapillary [75], squamous [164] and sarcomatoid [75], all of which are consistently associated with locally-advanced disease and worse outcome [73]. Patients harbouring pathological subtypes should be proposed RNU after a shared-decision process due to the higher risk of progression.

6.1.2.4 Lymph node involvement

Patients with nodal metastasis experience poor survival after surgery [165]. Lymph node density (cut-off 30%) and extranodal extension are powerful predictors of survival outcomes in N+ UTUC [166-168]. Lymph node dissection (LND) performed at the time of RNU allows for optimal tumour staging, although its curative role remains controversial [167, 169-172].

6.1.2.5 Lymphovascular invasion

Lymphovascular invasion (LVI) is present in approximately 20% of invasive UTUCs and is an independent predictor of survival [173-175]. Lymphovascular invasion status should be specifically reported in the pathological reports of all UTUC specimens [176, 177].

6.1.2.6 Surgical margins

Positive soft tissue surgical margin is associated with a higher risk of disease recurrence after RNU. Pathologists should look for and report positive margins at the level of ureteral transection, bladder cuff, and around the tumour [178].

6.1.2.7 Other pathological factors

Extensive tumour necrosis (> 10% of the tumour area) is an independent prognostic predictor in patients who undergo RNU [179]. Where neoadjuvant treatment was given, pathological downstaging is associated with better OS [180, 181]. The architecture of UTUC, as determined from pathological examination of RNU specimens, is also a strong prognosticator with sessile growth pattern being associated with worse outcome [182-184]. Concomitant CIS in organ-confined UTUC and a history of bladder CIS are associated with a higher risk of recurrence and cancer-specific mortality [185, 186]. Macroscopic infiltration or invasion of peri-pelvic adipose

tissue confers a higher risk of disease recurrence after RNU compared to microscopic infiltration of renal parenchyma [71, 187].

6.1.3 Molecular markers

Because of the rarity of UTUC, the main limitations of molecular studies are their retrospective design and, for most studies, small sample size. None of the investigated markers have been validated to support their introduction in daily clinical decision making [79, 143].

6.2 Risk stratification for clinical decision making

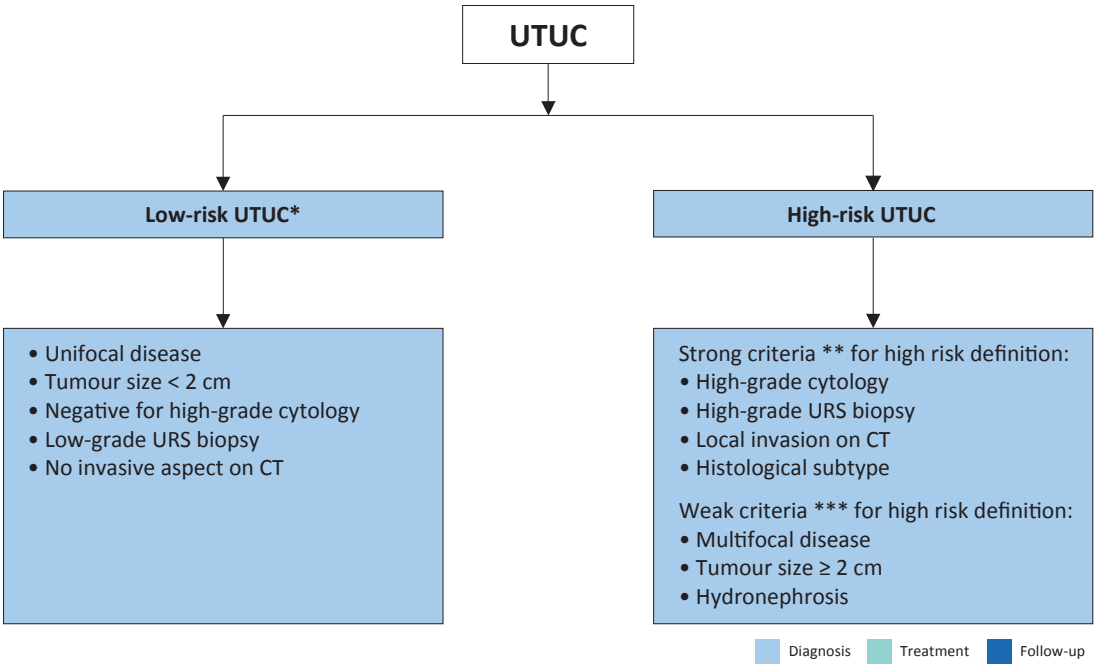
As tumour stage is difficult to assess clinically in UTUC, it is useful to stratify patients according to the low- and high risk of progression in order to identify those who are likely to benefit from kidney-sparing treatment and those who should be treated by radical nephroureterectomy [188, 189]. The factors to consider for the risk stratification are presented in Figure 6.1.

The level of evidence to consider individually 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 discuss the therapeutic strategy (kidney-sparing strategy or RNU).

Pre-RNU models aiming at predicting which patient has > pT2 /non-organ-confined disease have been published [190-194]. Several risk stratification models have been assessed with the main aim to identify better patients eligible for kidney-sparing surgery [188, 189, 195-197].

Prognostic nomograms based on pre-operative factors and post-operative pathological characteristics are also available [169, 192, 198-203] and may be used when counselling patients regarding follow-up and administration of peri-operative chemotherapy. Nevertheless, despite a moderate to good discrimination accuracy, severe heterogeneity discourages its use in systematic ways.

Figure 6.1: Risk stratification of non-metastatic UTUC according to the risk of progression to a> pT2 /non-organ-confined disease



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

6.3 Bladder recurrence

A meta-analysis of available data has identified significant predictors of bladder recurrence after RNU [22]. Three categories of predictors for increased risk of bladder recurrence were identified:

1. Patient-specific factors such as male gender, previous BC, smoking and pre-operative chronic kidney disease.
2. Tumour-specific factors such as positive pre-operative urinary cytology, tumour grade, ureteral location, multifocality, tumour diameter, invasive pT stage, and necrosis [204, 205].
3. Treatment-specific factors such as laparoscopic approach, extravesical bladder cuff removal, and positive surgical margins [22].

In addition, the use of diagnostic URS has been associated with a higher risk of developing bladder recurrence after RNU [206, 207]. Based on low-level evidence only, a single dose of intravesical chemotherapy after diagnostic/therapeutic ureteroscopy of non-metastatic UTUC has been suggested to lower the rate of intravesical recurrence, similarly to that after RNU [22].

6.4 Summary of evidence and recommendation for the prognosis of UTUC

Summary of evidence	LE
Important prognostic factors for risk stratification include tumour size, stage, grade, multifocality, hydronephrosis and different histological subtypes.	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 on imaging should be discussed in a multidisciplinary team prior to the initiation of treatment.

7.1 Localised low-risk disease

7.1.1 General considerations on kidney-sparing surgery

Kidney-sparing surgery for low-risk UTUC reduces the morbidity associated with radical nephroureterectomy (e.g., loss of kidney function), without compromising oncological outcomes [208]. In low-risk cancers, it is the preferred approach as survival is similar to that after RNU [208]. 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 clinically low-risk cancer [209, 210]. A flexible ureteroscope is useful in the management of pelvicalyceal tumours [211]. The patient should be informed of the need and be willing and able to comply with an early second-look URS [212] and stringent surveillance; complete tumour resection or destruction is necessary [212]. 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 [213]. A systematic review reported comparable survival outcomes after endoscopic treatment to radical nephroureterectomy at the cost of higher local recurrence rates and repeated interventions, but also with some uncertainties about long-term renal preservation after endoscopic treatment [214].

*7.1.3 **Percutaneous access***

Percutaneous management can be considered for low-risk UTUC in the renal pelvis [209, 215]. 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 [210, 215]. Moreover, a risk of tumour seeding remains with percutaneous access [215].

*7.1.4 **Ureteral resection***

Segmental ureteral resection with adequate margins provides sufficient pathological specimens for staging and grading while preserving the ipsilateral kidney. Segmental resection of the proximal two-thirds of ureter is associated with higher failure rates than for the distal ureter [216, 217].

Distal ureterectomy with ureteroneocystostomy is indicated for low-risk tumours in the distal ureter that cannot be completely removed endoscopically [199, 216, 218]. A total ureterectomy with an ileal-ureteral substitution or renal autotransplantation with pyelocystostomy is technically feasible, but only in selected cases when a renal-sparing procedure is mandatory and the tumour is low risk [219, 220].

*7.1.5 **Chemo-ablation***

A single-arm phase III trial including 71 patients with biopsy-proven low-grade UTUC 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%) [221]. 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 the 41 patients with complete response, 29 received at least one maintenance instillation (median of 6), 23/41 (56%) remained disease free at one year [221].

*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 [186, 222]. 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 [223-226].

A systematic review and meta-analysis assessing the oncologic outcomes of patients with papillary UTUC or CIS of the upper tract treated with kidney-sparing surgery and adjuvant endocavitary treatment analysed the effect of adjuvant therapies (i.e., chemotherapeutic agents and/or immunotherapy with BCG) after kidney-sparing surgery for papillary non-invasive (Ta–T1) UTUCs and BCG for the treatment of upper tract CIS, finding no difference between the method of drug administration (antegrade vs. retrograde vs. combined approach) in terms of recurrence, progression, CSS, and OS; 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 [227]. The analyses were based on retrospective small studies suffering from publication and reporting bias.

Recent evidence suggests that early single adjuvant intracavitary upper tract instillation of mitomycin C in patients with low-grade UTUC might reduce the risk of local recurrence [228]. The authors report limited complications related to the instillations but propose a retrograde pyelography before instillations are commenced to exclude contrast extravasation. This concept will need further evaluation in a randomised context [228].

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 **Recommendation for kidney-sparing management of localised low-risk UTUC***

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

7.2 Localised high-risk disease

*7.2.1 **Radical nephroureterectomy***

7.2.1.1 Surgical approach

7.2.1.1.1 Open radical nephroureterectomy

Open RNU with bladder cuff excision is the standard treatment of high-risk UTUC, regardless of tumour location [13]. Radical nephroureterectomy must be performed according to oncological principles preventing tumour seeding [13]. Section 7.2.5 lists the recommendations for RNU.

7.2.1.1.2 Minimal invasive radical nephroureterectomy

Retroperitoneal metastatic dissemination and metastasis along the trocar pathway following manipulation of large tumours in a pneumoperitoneal environment may occur [229, 230]. Several precautions may lower the risk of tumour spillage:

1. avoid entering the urinary tract, except when performing a bladder cuff excision and only after prior clipping of the ureter and complete drainage of the bladder;
2. avoid direct contact between instruments and the tumour;
3. perform the procedure in a closed system. Avoid morcellation of the tumour and use an endobag for tumour extraction;
4. the kidney and ureter must be removed *en bloc* with the bladder cuff;
5. in invasive or large (T3/T4 and/or N+/M+) tumours an open approach is favoured, as the oncological outcomes may be better compared to minimally-invasive RNU [231, 232].

Laparoscopic RNU is safe in experienced hands when adhering to strict oncological principles. There is a tendency towards equivalent oncological outcomes after laparoscopic vs. open RNU [230, 233-236]. One prospective randomised study has shown that laparoscopic RNU is inferior to open RNU for non-organ- confined UTUC. However, this was a small trial (n = 80) [232]. Oncological outcomes after RNU have not changed significantly over the past three decades despite staging and surgical refinements [237]. In a population-based data set, a hospital volume of > 6 patients per year treated with RNU showed improvement of short-term outcomes (30- and 90-day mortality) and overall long-term survival [238]. A robot-assisted laparoscopic approach can be considered allowing comparable peri operative benefit as standard laparoscopic surgery [239-241], with data suggesting oncologic equivalence with the other approaches [242-244]; however, the risk of intravesical recurrence may be increased with both laparoscopic and robotic RNU compared to the open approach [245].

7.2.1.1.3 Bladder cuff management

Resection of the distal ureter and its orifice is performed because there is a considerable risk of tumour recurrence in this area and in the bladder [22, 216, 246-248]. Several techniques have been considered to simplify distal ureter resection, including the pluck technique, stripping, transurethral resection of the intramural ureter, and intussusception. None of these techniques has convincingly been shown to be equal to complete bladder cuff excision [23, 246].

7.2.1.1.4 Lymph node dissection

The use of a LND template is likely to have a greater impact on patient survival than the number of removed LNs [249]. Template-based and completeness of LND improves CSS in patients with muscle-invasive disease and reduces the risk of local recurrence [250]. Even in clinically [251] and pathologically [252] node-negative patients, LND improves survival. The risk of LN metastasis increases with advancing tumour stage [170]. Lymph node dissection appears to be unnecessary in cases of TaT1 UTUC because of the low risk of LN metastasis [253-256], however, tumour staging is inaccurate pre-operatively; therefore a template-based LND should be offered to all patients who are scheduled for RNU for high-risk UTUC. The templates for LND have been described [250, 257, 258].

*7.2.2 **Distal ureterectomy***

Distal ureterectomy for high-risk UTUC in the distal ureter only seems to be associated with similar oncological outcomes as RNU [208, 259]. This procedure can be performed with concomitant LN dissection. However,

given the low level of evidence, this approach should only be currently used in highly selected cases where the benefits may be greater than the potential risks.

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

Kidney-sparing surgery, including ureteroscopy or segmental ureterectomy, can be considered on a case-by- case basis for patients with high-risk UTUC with imperative indications such as solitary kidney, bilateral UTUC, 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 [208].

*7.2.4 **Peri-operative chemotherapy***

7.2.4.1 Neoadjuvant treatments

7.2.4.1.1 Chemotherapy

The primary advantage of neoadjuvant chemotherapy (NAC) is the ability to give cisplatin-based regimens when patients still have maximal renal function. Several retrospective studies evaluating the role of NAC have shown evidence of pathological downstaging and complete response rates at RNU [180, 260-263] with a direct impact on OS [194]. 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 [262, 264-266].

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 [267, 268]. 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 [269]. 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.

7.2.4.1.2 Immunotherapy

Only a small phase II study including 10 patients with high-risk UTUC evaluated the efficacy of pembrolizumab in the neoadjuvant setting [270]. However, no pathological response was observed and one treatment-related death was reported. Thus, there is currently no evidence to support the use of neoadjuvant immunotherapy for high-risk UTUC.

7.2.4.2 Adjuvant treatments

7.2.4.2.1 Bladder instillations

The rate of bladder recurrence after RNU for UTUC is 22–47% [189, 246]. Two prospective randomised trials [271, 272] and two meta-analyses [273, 274] 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 in case of concerns about drug extravasation. All studies showed a very low risk of adverse events. Intravesical chemotherapy has also been safely given at the time of RNU prior to bladder cuff opening, removing the need for a post- operative cystogram, but with low level data for efficacy [275].

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 [276]. Whilst there is no direct evidence supporting the use of intravesical chemotherapy instillation of chemotherapy after kidney-sparing surgery, single- dose chemotherapy might also be effective in that setting as well. 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 [277].

7.2.4.2.2 Systemic Chemotherapy

A phase III multicentre prospective RCT (n = 261) evaluating the benefit of four cycles of adjuvant gemcitabine-platinum combination chemotherapy initiated within 90 days after RNU vs. surveillance has reported a significant improvement in disease-free survival (DFS) in patients with pT2–pT4, N (any) or 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) [278]. 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. 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 [279, 280]. A review of peri-operative predictors of decline in renal function after RNU showed three month GFR levels of around 50 mls/min [281]. 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.

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 [282]. However, whilst histological subtypes of UTUC exhibit different survival rates in retrospective studies, adjuvant chemotherapy should be considered where 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***

7.2.4.2.3 Immunotherapy

In a phase III, multicentre, double-blind RCT involving patients with high-risk muscle-invasive UC who had undergone radical surgery (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 [283]. The patient population predominantly consisted of BC patients post-radical cystectomy, with an additional smaller cohort of patients with UTUC post-RNU. The median recurrence-free survival outside the urothelial tract in the entire intention-to-treat population was 22.9 months for nivolumab and 13.7 months for placebo. Treatment-related adverse events > 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 with 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 [284].

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 [285].

7.2.4.2.4 Radiotherapy

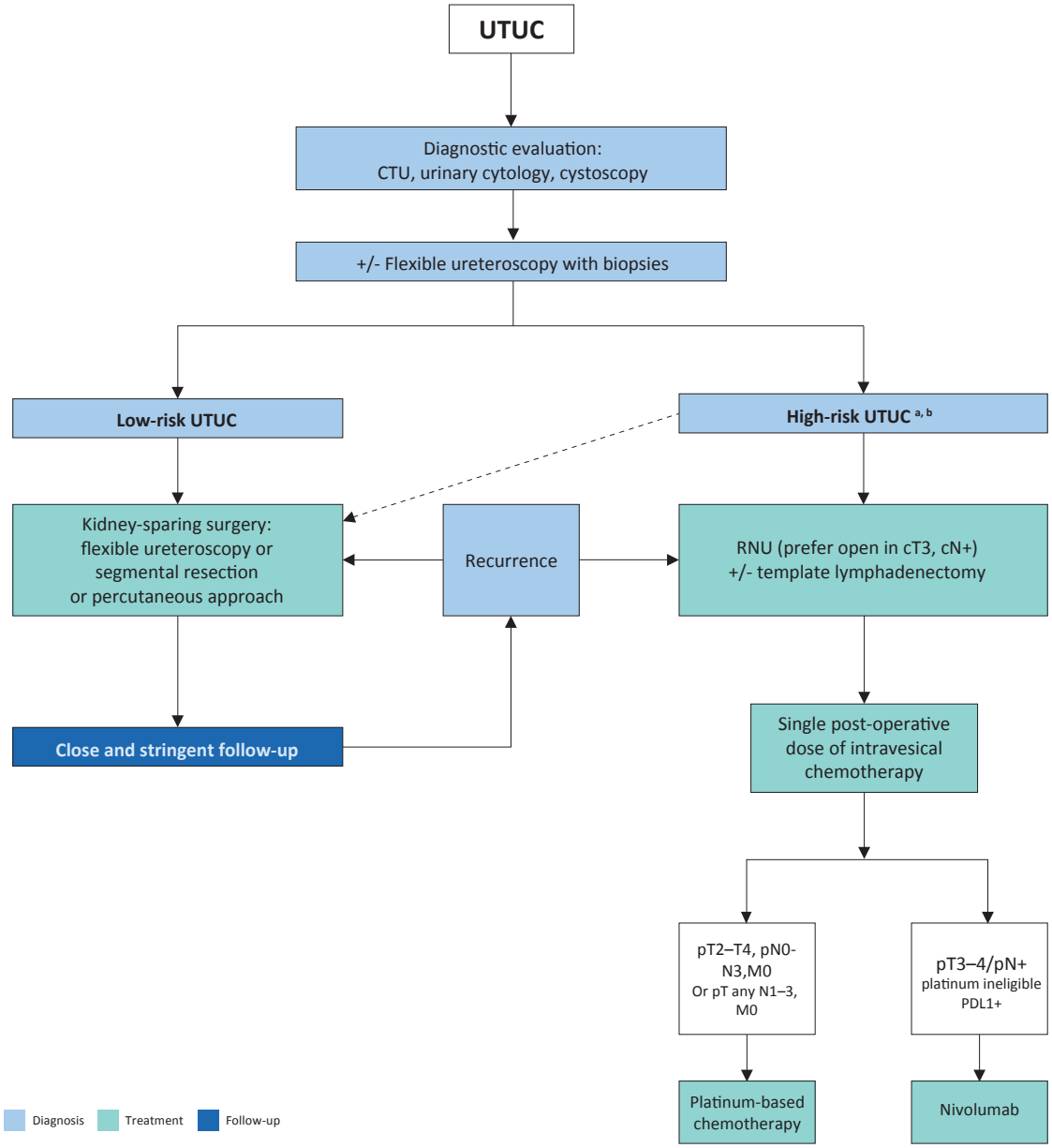
Adjuvant radiation therapy has been suggested to control loco-regional disease after surgical removal. The data remains controversial and insufficient for conclusions [286-289]. Moreover, its added value to chemotherapy remains questionable [288].

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

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

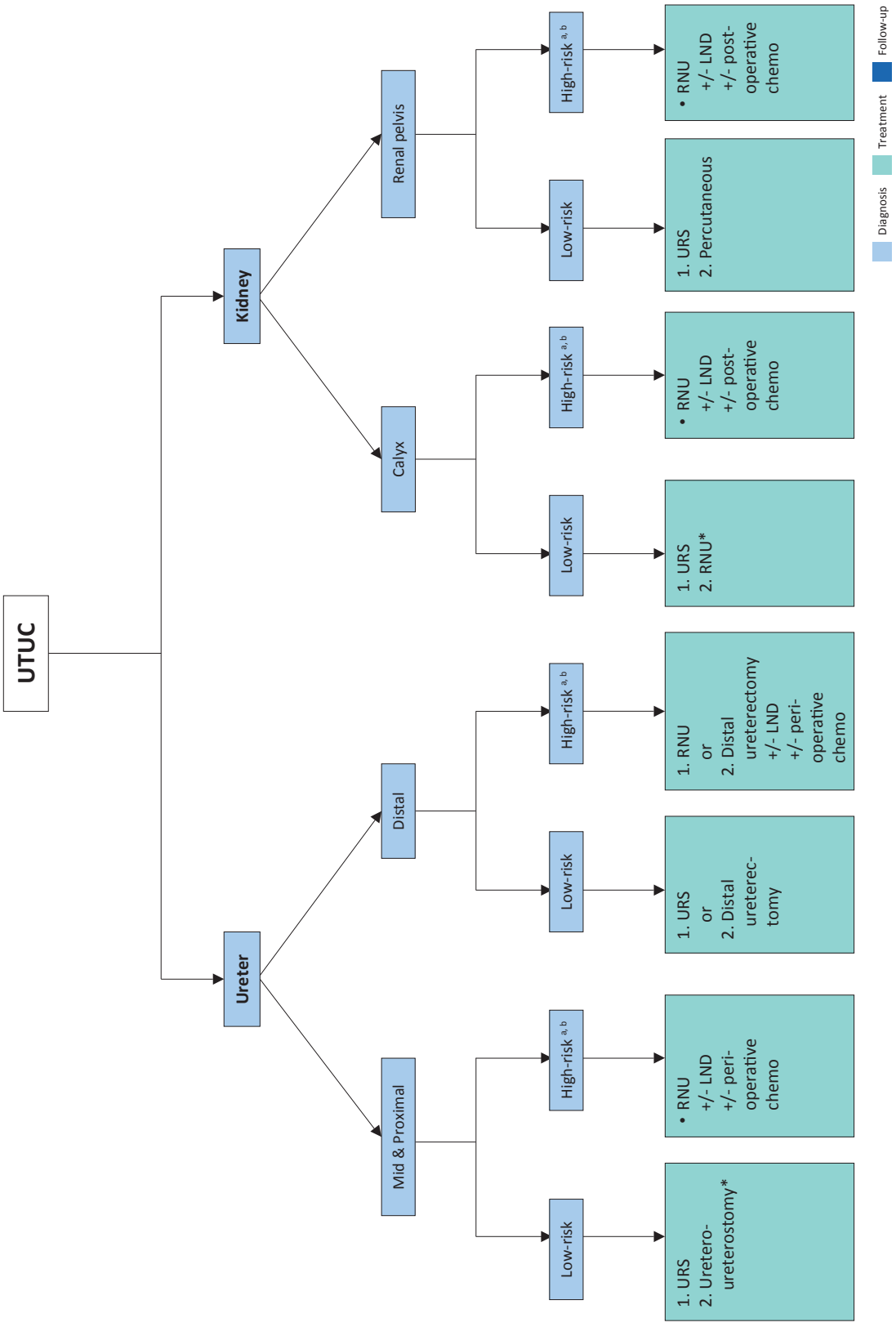
Recommendations	Strength rating
Perform radical nephroureterectomy (RNU) in patients with high-risk non-metastatic upper tract urothelial carcinoma (UTUC).	Strong
Perform open RNU in non-organ confined UTUC.	Weak
Perform a template-based lymphadenectomy in patients with high-risk non-metastatic UTUC.	Weak
Offer adjuvant platinum-based chemotherapy after RNU to 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 BC.	Strong
Discuss adjuvant nivolumab with 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
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***

Evidence is lacking regarding the optimal management of clinical node-positive disease. Patients with clinically N+ UTUC should be offered downstaging first-line platinum-based chemotherapy. In patients whose cancer responds or who have stable disease, maintenance avelumab can be offered, especially in cN2 disease [290]. Depending on the extent of the nodal disease (i.e., cN1/N2) surgical resection with LN dissection can be discussed in a multidisciplinary team and with the patient when responding on after initial systemic therapy. In patients whose cancer progress, second-line treatment can be offered, similar to metastatic disease [291, 292].

*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% (versus 44%) and CR 29% . OS benefit was seen across sub groups 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 is not yet known.

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 [293]. 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 [293].

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 [294]. 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 were thus not previously recommended [295-297]. 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 v 18.9 months HR 0.78 (0.63-0.96) as well as median PFS (7.9 months versus 7.6 months HR 0.72 (0.59-0.88). Objective RR were 57.6% compared with 43.1 % for chemotherapy alone [298]. 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 [299], 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 [300].

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 4 to 6 cycles of gemcitabine plus cisplatin or carboplatin (started within 10 weeks of completion of first-line platinum-based chemotherapy) significantly prolonged

OS as compared to best supportive care alone in those patients with advanced or metastatic UC who did not experience disease progression during, or responded to, first-line chemotherapy (HR: 0.69; 95% CI: 0.56–0.86) [290, 301]. 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) [302].

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 [303]. 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 [304]. Median OS in the overall cohort was 15.9 months and treatment-related toxicity was in line with previous studies [296].

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.

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) [305]. 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 [306].

Other immunotherapies such as nivolumab [307], avelumab [308, 309] and durvalumab [310] have shown objective response rates ranging from 17.8% [310] to 19.6% [307] 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 [309].

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 [311]. 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 [312].

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) [313]. 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 [314]. As the rate of activating alterations of FGFR3 is higher in UTUC than in bladder cancer [315] 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.

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 [316]. 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) [317].

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 [318].

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 [319]. 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

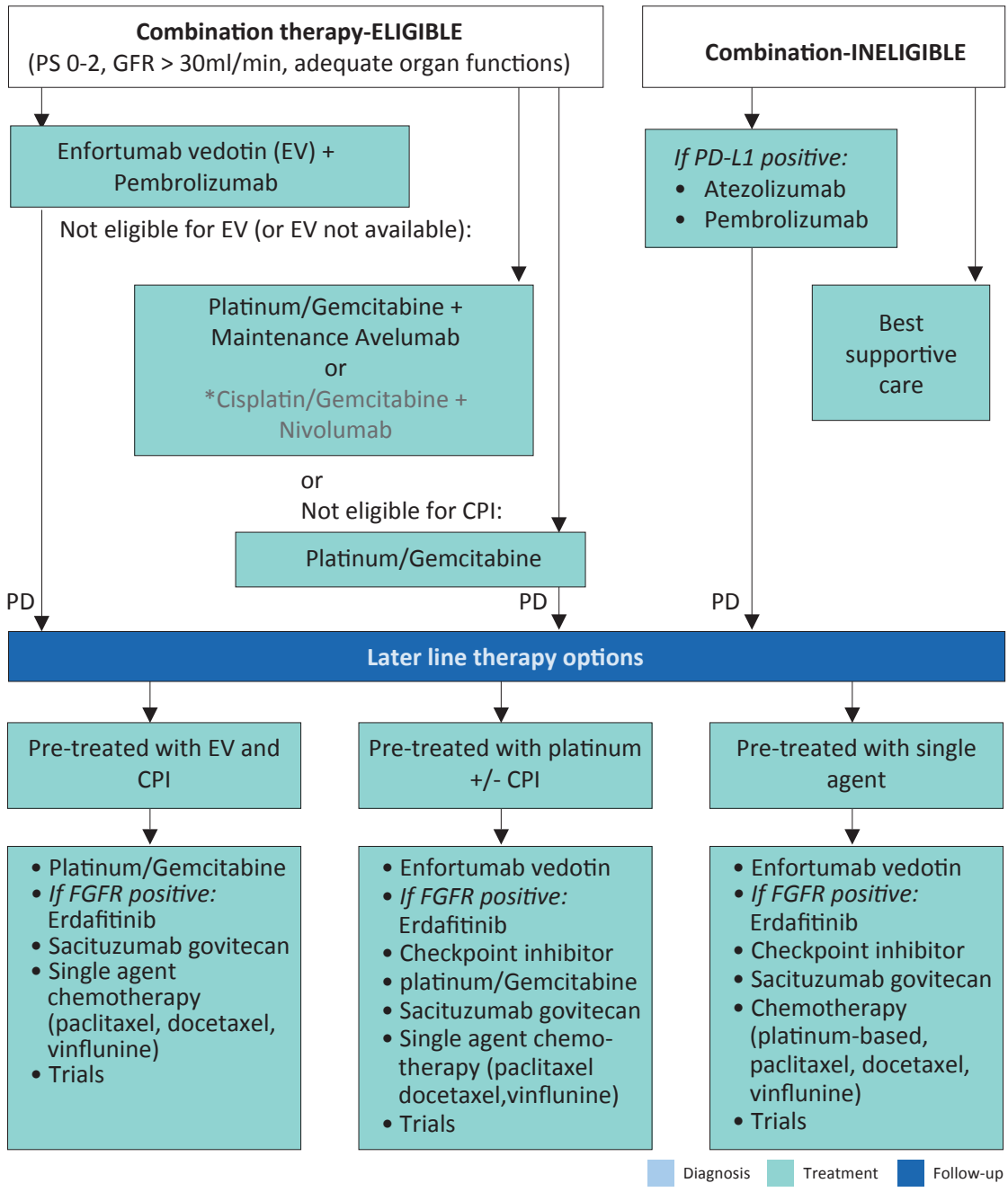
Data regarding RNU in the metastatic setting are lacking with mainly retrospective observational studies [320-322].

Although evidence remains very limited, RNU may be associated with CSS [321, 323, 324] and OS benefit in selected patients, especially those fit enough to receive cisplatin-based chemotherapy [320, 321]. It is noteworthy that these benefits may be limited to those patients with only one metastatic site [321]. 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 [26, 124].

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 [325-329]. 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*
EV = enfortumab vedotin; FGFR = fibroblast growth factor receptor; GFR = glomerular filtration rate; PS = performance status; CPI=checkpoint inhibitor; 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
Enfortmab vedotin + Pembrolizumab offers an overall survival benefit compared to gemcitabine-cisplatin in the 1st 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 1st 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

Test UTUC patients for FGFR alterations (FGFR2/3 mutations or FGFR3 fusions) prior to erdafitinib treatment.	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 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 9 months later and yearly cystoscopies for 5 years [330]. 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 [331].

When RNU has been performed for high-risk tumours, stringent follow-up is mandatory to detect metachronous bladder tumours (probability increases over time [332]), local recurrence, and distant metastases. The risk of bladder recurrences and other-site recurrences decreases 4 years after RNU, suggesting that less vigorous annual cystoscopies and cross-sectional imaging including CT urographies thereafter may apply [333]. For high risk, please consult the recommendations.

After kidney-sparing management for low-risk UTUC, and where no subsequent upstaging or upgrading occurred after the early second-look ureteroscopy after 6-8 weeks [212] or was found in the resection specimen after segmental ureteric resection, cystoscopy and CT-urography should be carried out at 3 and 6 months, and then yearly for 5 years. The risk for bladder recurrences beyond 5 years is limited (6%) [334].

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 [211, 335, 336] and progression following RNU, even beyond 5 years [337].

Surveillance regimens are based on CT urography, cystoscopy and urinary cytology [332, 338]. 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 [339].
- The effect of the Paris System on sensitivity and specificity of voided and selective urinary cytology during follow-up of UTUC, especially in high-risk tumours [340].
- 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 of followed long-term given the inadequacy of surveillance based on urinalysis for nonvisible haematuria [341] and urine cytology [342], 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	
Perform cystoscopy and urinary cytology at 3 months. If negative, repeat subsequent cystoscopy and cytology every 3 months for a period of 2 years, and every 6 months thereafter until 5 years, and then yearly.	Weak
Perform computed tomography (CT) urography and chest CT every 6 months for 2 years, and then yearly.	Weak
After kidney-sparing management	
Low-risk tumours	
Perform cystoscopy and CT urography at 3 and 6 months, and then yearly for 5 years.	Weak
Perform ureteroscopy (URS) at 3 months if no second-look ureteroscopy was performed.	Weak
High-risk tumours	
Perform second-look URS and cytology in 6 weeks. If no residual tumour follow similar follow-up principles as for high-risk disease treated with radical nephroureterectomy.	Weak

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10. CONFLICT OF INTEREST

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

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