Guidelines on

Urothelial Carcinomas of the Upper Urinary Tract

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European Association of Urology

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1. INTRODUCTION

The latest European Association of Urology (EAU) guidelines on upper urinary tract tumours known as upper tract urothelial carcinomas (UTUCs) were published in 2013 (1). The EAU Guidelines Working Panel for UTUCs has prepared the current guidelines to provide evidence-based information for the clinical management of these rare tumours and to help clinicians incorporate these recommendations into their practice. The current update is based on a structured literature search.

2. METHODOLOGY

2.1 Data identification

A Medline search was performed on urothelial malignancies and UTUC management using combinations of the following terms: *urinary tract cancer; urothelial carcinoma; upper urinary tract; renal pelvis; ureter; chemotherapy; nephroureterectomy; adjuvant treatment; neoadjuvant treatment; recurrence; risk factors; nomogram; and survival*, with a cut-off date of November 2013. The publications concerning UTUCs were mostly retrospective, including some large multicentre studies. Due to the scarcity of randomized data, articles were selected for these guidelines based on the following criteria: evolution of concepts, intermediate- and long-term clinical outcomes, study quality, and relevance. Older studies were included selectively if they were historically relevant or if data were scarce in recent publications. To facilitate evaluation of the quality of information provided, levels of evidence (LE) and grades of recommendation (GR) were inserted according to general principles of evidence-based medicine (EBM) (2).

2.2 Publication history

A first guidelines publication on upper urinary tract tumours was presented in 2004 (3). This document was updated and included in the EAU Guidelines compilation print in 2013. The current 2014 publication presents a limited update of the 2013 document.

2.3 Potential conflict of interest statement

The expert panel have submitted potential conflict of interest statements, which can be viewed on the EAU website: http://www.uroweb.org/guidelines/online-guidelines/.

3. EVIDENCE SYNTHESIS

3.1 Epidemiology

Urothelial carcinomas are the fourth most common tumours after prostate (or breast), lung and colorectal cancer (4,5). They can be located in the lower urinary tract (bladder and urethra) or upper urinary tract (pyelocaliceal cavities and ureter). Bladder tumours account for 90-95% of urothelial carcinomas (UCs) and are the most common malignancy of the urinary tract (1,5). However, UTUCs are uncommon and account for only 5-10% of UCs (4,6). The estimated annual incidence of UTUCs in Western countries is about two new cases per 100,000 inhabitants. Pyelocaliceal tumours are about twice as common as ureteral tumours. In 17% of cases, concurrent bladder cancer is present (7). Recurrence of disease in the bladder occurs in 22-47% of UTUC patients (8-10), whereas recurrence in the contralateral upper tract is observed in 2-6% (11,12).

The natural history of UTUCs differs from that of bladder cancer: 60% of UTUCs are invasive at diagnosis compared with only 15-25% of bladder tumours (13,14). UTUCs have a peak incidence in people in their 70s and 80s and are three times more common in men than in women (15,16).

There are familial/hereditary cases of UTUCs linked to hereditary non-polyposis colorectal carcinoma (HNPCC) (17). Among patients with UTUCs, HNPCC can be screened during a medical interview (18). There is a suspicion of hereditary UTUC if the patient is < 60 years of age, has a personal history of an HNPCC-associated cancer, a first-degree relative aged < 50 years with HNPCC-associated cancer, or two first-degree relatives with HNPCC-associated cancer (18). These patients should undergo DNA sequencing to identify hereditary cancers that have been misclassified as sporadic cancers by insufficient clinical data (19). The presence of other HNPCC-associated cancers should also be evaluated. These patients should be closely monitored and genetic counselling is advocated (17,19).

3.2 Risk factors

Many environmental factors contribute to the development of UTUCs (20,21). Some are similar to those associated with bladder cancer, whereas others are more specific for UTUC. Tobacco and occupational exposure remain the principal exogenous risk factors for developing these tumours. Tobacco exposure increases the relative risk of developing UTUC from 2.5 to 7 (20,21). UTUC 'amino' tumours' are related to occupational exposure to certain aromatic amines. These aromatic hydrocarbons are used in many industries (e.g. dyes, textiles, rubber, chemicals, petrochemicals and coal). They are responsible for the carcinogenicity of certain chemicals, including benzidine and β-naphthalene. These two chemicals have been banned since the 1960s in most industrialized countries. In most cases, UTUCs are secondary to an amino tumour of the bladder. The average duration of exposure needed to develop a UTUC is approximately 7 years, with a latency period of about 20 years following termination of exposure. The estimated risk (odds ratio) of developing UC after exposure to aromatic amines is 8.3 (21,22). Upper urinary tract tumours resulting from phenacetin consumption almost disappeared after the product was banned in the 1970s (21).

Although the incidence of Balkan endemic nephropathy is declining, roles have been proposed for aristolochic acid and the consumption of Chinese herbs in the pathophysiology and induction, respectively, of this nephropathy (23-26). Several studies have revealed the carcinogenic potential of aristolochic acid contained in *Aristolochia fangchi* and *Aristolochia clematis* (plants endemic to the Balkans). This acid contains a set of highly toxic nitrophenolate derivatives that exhibit a powerful mutagenic action due to their ability to make up covalent links with cell DNA. The aristolochic acid derivative d-aristolactam causes a specific mutation in the p53 gene at codon 139. This mutation is very rare in the non-exposed population and occurs mainly in patients with nephropathy due to Chinese herbs or Balkan endemic nephropathy, who present with UTUC (21,23,24).

A high incidence of UTUC has been described in Taiwan, especially in the population on the Southwest coast of the island, and represents 20-25% of UCs in the region (21,24). The association of UTUC with blackfoot disease and arsenic exposure remains unclear in this patient population (21,24). Differences in the ability to counteract carcinogens may contribute to host susceptibility and the risk of developing. A particular genotype may sometimes confer protection for an organ and increase the risk for another. In addition, UTUC may share some risk factors or molecular disruption pathways with bladder UC, although each condition still has its own specific features. Certain genetic polymorphisms are associated with an increased risk of cancer or faster disease progression, which introduces variability in the inter-individual susceptibility to the risk factors previously mentioned. Only two polymorphisms specific to UTUC have been reported so far (27,28). A variant allele, SULT1A1*2, which reduces sulfotransferase activity, and a polymorphism located at the T allele of rs9642880 on chromosome 8q24 enhance the risk of developing UTUC.

3.3 Histology and classification

*3.3.1 **Histological types***

More than 95% of UCs are derived from the urothelium and correspond to UTUCs or bladder tumours (13,29). With regard to UTUCs, morphological variants have been described that are more often observed in urothelial kidney tumours. These variants always correspond to high-grade tumours, and such UCs are associated with one of the following variants: micropapillary, clear cell, neuroendocrine or lymphoepithelial (29,30). Collecting-duct carcinoma can have similar characteristics to UTUC because of its common embryological origin (31). Upper urinary tract tumours with pure non-urothelial histology are exceptions (32,33) but variants can be seen in nearly 25% of cases (34). Squamous cell carcinomas of the upper urinary tract represent < 10% of pyelocaliceal tumours and are even rarer within the ureter. Squamous cell carcinoma of the urinary tract is associated with chronic inflammatory and infectious diseases arising from stones in the urinary tract (29,30). Other histological subtypes are adenocarcinomas (< 1%), small cell carcinomas, and sarcomas.

*3.3.2 **Classification***

The classification and morphology of UTUCs are similar to those of bladder carcinomas (13). It is possible to distinguish between non-invasive papillary tumours (papillary urothelial tumours of low malignant potential, low-grade papillary UC, high-grade papillary UC), flat lesions (carcinoma *in situ* [CIS]), and invasive carcinomas. All variants of urothelial tumours described in the bladder can also be observed in the upper urinary tract (34).

3.3.2.1 Tumour Node Metastasis staging

Table 1 presents the Union Internationale Contre le Cancer (UICC) 2009 Tumour Node Metastasis (TNM) classification used throughout these guidelines (35). According to the TNM classification, the regional lymph nodes that should be considered are the hilar, abdominal para-aortic, and paracaval nodes, and, for the ureter, the intrapelvic nodes. Laterality does not affect the N classification.

There might be an interest in a renal pelvic pT3 subclassification to discriminate between microscopic infiltration of the renal parenchyma (pT3a) versus macroscopic infiltration or invasion of peripelvic adipose tissue. pT3a and pT3b have been suggested as a subclassification (34,36). pT3b UTUCs are more likely to have aggressive pathological features and to have a higher risk of recurrence (34,36).

Table 1: TNM classification 2009 for UTUC (35)*

T - Primary tumour	
TX	Primary tumour cannot be assessed
T0	No evidence of primary tumour
Ta	Non-invasive papillary carcinoma
Tis	CIS
T1	Tumour invades subepithelial connective tissue
T2	Tumour invades muscle
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 but not more than 5 cm in the greatest dimension or multiple lymph nodes, none more than 5 cm in greatest dimension
N3	Metastasis in a lymph node more than 5 cm in greatest dimension
M - Distant metastasis	
M0	No distant metastasis
M1	Distant metastasis

**All EAU guidelines advocate the TNM system of tumour classification.*

3.3.2.2 Tumour grade

Until 2004, the most common classification used was the World Health Organization (WHO) classification of 1973, which distinguished only three grades (G1, G2 and G3) (37). In recent years, molecular biological data have allowed for further distinction between different tumour groups and the development of a new classification system that better reflects the potential growth of these tumours (38). Thus, the 2004 WHO classification now takes histological data into account to distinguish among three groups of non-invasive tumours: papillary urothelial neoplasia of low malignant potential; low-grade carcinomas; and high-grade carcinomas. There are almost no tumours of low malignant potential in the upper urinary tract (29,30).

3.4 Symptoms

The diagnosis of UTUC may be fortuitous or related to the exploration of symptoms. The symptoms are generally restricted (39). The most common symptom of UTUC is gross or microscopic haematuria (70-80%) (40). Flank pain occurs in 20-40% of cases, and a lumbar mass is present in 10-20% (41,42). However, systemic symptoms (altered health condition including anorexia, weight loss, malaise, fatigue, fever, night sweats, or cough) associated with UTUC should prompt consideration of a more rigorous metastatic evaluation (41,42).

3.5 Diagnosis

3.5.1 ***Imaging***

3.5.1.1 Computed tomography urography

Computed tomography (CT) urography is the imaging technique with the highest diagnostic accuracy for UTUC and has replaced intravenous excretory urography and ultrasonography as the first-line imaging test for investigating high-risk patients (40). The sensitivity of CT urography for UTUC is reported to range from 0.67 to 1.0 and specificity from 0.93 to 0.99 depending on the technique used (43-50). Attention to technique is therefore very important for optimum results.

CT urography of the urinary tract acquires at least one image series during the excretory phase, usually 10-15 minutes, following the administration of intravenous contrast medium (51). Rapid acquisition of thin sections allows high-resolution isotropic images to be produced that can be viewed in multiple planes to assist with diagnosis without degradation of resolution (52,53).

CT urography can detect wall thickening of the renal pelvis or ureter, which is a sign of UTUC, even when there is no luminal mass effect. Flat lesions are not detectable unless they exert a mass effect or cause urothelial thickening (54). The secondary sign of hydronephrosis upon imaging in the presence of UTUC is associated with advanced pathological disease and poorer oncological outcomes (51,55).

3.5.1.2 Magnetic resonance imaging

Magnetic resonance (MR) urography is indicated in patients who cannot undergo CT urography usually when radiation or iodinated contrast media are contraindicated (56). The sensitivity of MR urography is 75% after contrast injection for tumours < 2 cm (56). Magnetic resonance urography with certain gadolinium-based contrast media is contraindicated in selected patients with severe renal impairment (< 30 mL/min creatinine clearance), due to the risk of nephrogenic systemic fibrosis.

CT urography is generally preferred to MR urography for diagnosing UTUCs in terms of greater diagnostic accuracy, lower cost, and greater patient acceptability.

3.5.2 ***Cystoscopy and urinary cytology***

Positive urine cytology is highly suggestive of UTUC when bladder cystoscopy is normal and provided that CIS of the bladder or prostatic urethra has been largely excluded (e.g. by biopsies of any suspicious lesion, possibly guided by photodynamic diagnosis) (13,57). Cytology is less sensitive for UTUC than for bladder tumours, even for high-grade lesions, and it should ideally be performed *in situ* (i.e. in the renal cavities) (58). Retrograde ureteropyelography (through a ureteral catheter or during ureteroscopy) remains an option for the exclusion of a tumour in the upper urinary tract (44,59). However, urinary cytology of the renal cavities and ureteral lumina should preferably be performed prior to application of larger amounts of contrast agent for retrograde ureteropyelography, because it may deteriorate cytological specimens.

The sensitivity of fluorescence *in situ* hybridization (FISH) for the identification of molecular abnormalities characterizing UTUCs parallels its performance in bladder cancer. However, its use may be limited by the preponderance of low-grade recurrent disease in the population undergoing surveillance and minimally invasive therapy for UTUCs (60,61). In addition, FISH appears to have limited surveillance value for upper UTUCs (60,61).

3.5.3 ***Diagnostic ureteroscopy***

Flexible ureteroscopy is used to visualize and biopsy the ureter, renal pelvis and collecting system with a technical success rate of nearly 95%. Such ureteroscopic biopsies can determine tumour grade in 90% of cases with a low false-negative rate, regardless of the sample size (62). Undergrading may occur from the diagnostic biopsy, making intensive follow-up a requirement if renal-sparing treatments are selected (63). Ureteroscopy also facilitates selective ureteral sampling for cytology *in situ* (59,64,65).

Flexible ureteroscopy is especially useful when there is diagnostic uncertainty, when conservative treatment is being considered, or in patients with a solitary kidney. If available, ureteroscopy and biopsy should be performed in the pre-operative assessment of any UTUC patient. Combining ureteroscopic biopsy grade, diagnostic imaging findings such as hydronephrosis, and urinary cytology, may help to decide between radical nephroureterectomy (RNU) and endoscopic treatment (64,66).

Technical developments in flexible ureteroscopes and the use of novel imaging techniques improve visualization and the diagnosis of flat lesions. Narrow band imaging appears to be the most promising technique but results are still preliminary (66,67). Table 2 lists the recommendations for diagnosis.

Table 2: Guidelines for the diagnosis of UTUC

Recommendations	GR
Urinary cytology	A
Cystoscopy to rule out a concomitant bladder tumour	A
CT urography	A
Diagnostic ureteroscopy and biopsy	C
Retrograde ureteropyelography	C

CT urography = computed tomography urography.

3.6 Prognostic factors

UTUCs that invade the muscle wall usually have a very poor prognosis. The 5-year specific survival is < 50% for pT2/pT3 and < 10% for pT4 (67,68). This section briefly describes the currently recognized prognostic factors (69).

3.6.1 Tumour stage and grade

According to the most recent classifications, the primary recognized prognostic factors are tumour stage and grade (64,69-71). Extranodal extension appears to be a powerful predictor of clinical outcomes in patients with UTUCs and positive lymph node metastases (72).

3.6.2 Age and sex

Sex is no longer considered an independent prognostic factor that influences UTUC mortality (15,69,73). However, patient age is considered to be an independent prognostic factor because older age at the time of RNU is associated with decreased cancer-specific survival (69,74) (LE: 3). However, chronological age alone should not be an absolute exclusion criterion for the treatment of potentially curable UTUC, but rather overall life expectancy. A significant proportion of elderly patients can still be cured with RNU (74), suggesting chronological age alone is an inadequate indicator of outcomes in older UTUC patients (74,75).

3.6.3 Ethnicity

There are differences in clinicopathological characteristics of tumours between Caucasian and Japanese patients. However, so far race and ethnicity are not recognized as independent factors for survival (76) (LE: 3).

3.6.4 Tumour location

According to the most recent findings, the initial location of the tumour within the upper urinary tract (e.g. ureter vs. renal pelvis) is a prognostic factor (77-79) (LE: 3) After adjustment for tumour stage, ureteral and multifocal tumours have a worse prognosis than renal pelvic tumours (69,78-81).

3.6.5 Tobacco consumption

Smoking intensity (long-term exposure) and being a smoker at diagnosis increases the risk for poor oncological outcomes (82-84) (LE: 3).

3.6.6 Lymphovascular invasion

Lymphovascular invasion is present in approximately 20% of UTUCs and is an independent predictor of survival (85,86). Lymphovascular invasion status should be systematically included and specifically reported in the pathological report of all RNU specimens (85,87) (LE: 3).

3.6.7 Surgical margins

Positive surgical margin after RNU appears to be a significant factor for developing subsequent UTUC metastases (LE: 3). Pathologists should look for, and report on, positive margins at the level of the ureteral transection, bladder cuff, and around the tumour if the tumour is > T2 (88).

3.6.8 Other factors

Extensive tumour necrosis is an independent predictor of clinical outcomes in patients who undergo RNU. Extensive tumour necrosis can be defined as > 10% of the tumour area (89,90) (LE: 3). The tumour architecture (e.g. papillary vs. sessile) of UTUCs appears to be associated with the prognosis after RNU. A sessile growth pattern is associated with the worst outcomes (91,92) (LE: 3). The presence of concomitant CIS in patients with organ-confined UTUC is associated with a higher risk of recurrent disease and cancer-specific mortality (93,94) (LE: 3). Similar to lower tract UC, concomitant CIS is an independent predictor of worse outcomes in organ-confined disease (95). A previous history of bladder CIS is associated with increased risk of recurrence and death from UTUCs (96) (LE: 3).

The American Society of Anesthesiologists (ASA) score also significantly correlates with cancer-specific survival after RNU (97) (LE: 3), but ECOG performance status correlates only with overall survival (98). Obesity and higher body mass index adversely affect cancer-specific outcomes in patients with UTUCs (99) (LE: 3).

*3.6.9 **Molecular markers***

Several research groups are working on UTUC characteristics and carcinogenesis pathways. Several studies have investigated the prognostic impact of various tissue-based markers related to cellular processes, such as cell adhesion (E-cadherin and CD24), cell differentiation (Snail and epidermal growth factor receptor), angiogenesis (hypoxia-inducible factor-1α and metalloproteinases), cell proliferation (Ki67), epithelialmesenchymal transition (snail), mitosis (Aurora-A), apoptosis (Bcl-2 and survivin) and vascular invasion (récepteur d'origine nantais, RON) and c-met protein (MET) (69,100-103). However, because of the rarity of the disease, the main limitations shared by these studies are their retrospective nature and their small sample size. Microsatellite instability (MSI) is an independent molecular maker used for tumour prognosis (104). In addition, MSI can help detect germ-line mutations, allowing for the detection of possible hereditary cancers (17).

To date, none of the markers has fulfilled the clinical and statistical criteria necessary to support their introduction in daily clinical decision making.

3.7 Predictive tools

Available accurate predictive tools are rare in UTUCs. There are two available models in a pre-operative setting: one for the prediction of locally advanced cancer that could guide the extent of lymph node dissection at the time of RNU (105); and one for selection of non-organ-confined UTUCs that are likely to benefit from nephroureterectomy (106). Additionally, two nomograms predict survival rates in a post-operative setting based on standard pathological features, the first developed by an international study group (107) and the second by a European population-only group (108).

3.8 Risk stratification

As with non-muscle invasive bladder cancer, it is necessary to 'risk stratify' UTUC cases (i.e., with a functional contralateral kidney) before treatment to identify those patients (and tumours) who are more suitable for conservative treatment rather than radical extirpative surgery (109). Based on the evidence available in UTUC, patients with a normal contralateral kidney can be classified at the time of diagnosis as having 'low-risk UTUC' or 'high-risk UTUC,' based on patient and/or clinical factors (Table 3).

Table 3: Risk stratification of UTUCs

High-risk UTUC	**Description**
Clinical factors	Hydronephrosis
	High-grade URS biopsy
	High-grade cytology
	Tumour size > 1 cm
	Invasive features on cross-sectional imaging
	Multifocal disease
	Failed endoscopic treatment of 'low-risk UTUC'
Patient factors	Previous bladder-UC and/or cystectomy
	Smoking
Low-risk UTUC	
Clinical factors	Low-grade ureteroscopic biopsy
	Low-grade cytology
	Tumour size < 1 cm
	No invasive features on cross-sectional imaging
	Unifocal disease
	Close follow-up possible and acceptable to patient

3.9 Treatment

3.9.1 ***Low-risk UTUC***

3.9.1.1 Conservative surgery

Conservative management of UTUCs can be considered in all imperative cases (renal insufficiency or solitary functional kidney) or in low-risk cases (when the contralateral kidney is functional) (see Table 3) (110-112) (LE: 3). Conservative surgery for low-risk UTUCs (Table 4) allows preservation of the upper urinary renal unit while sparing the patient the morbidity associated with open radical surgery. The choice of technique depends on technical constraints, the anatomical location of the tumour, and the experience of the surgeon.

3.9.1.1.1 Ureteroscopy

Endoscopic ablation can be considered in highly selected cases and in the following situations (113-1145):

- A flexible rather than a rigid ureteroscope, laser generator (134), and pliers (pluck) for biopsies are available (114,117) (LE: 3).
- The patient is informed of the need for closer, more stringent, surveillance.
- A complete resection of the tumour is strongly advocated.

However, there is a risk of understaging and undergrading the disease with pure endoscopic management.

3.9.1.1.2 Segmental resection

Segmental ureteral resection with wide margins provides adequate pathological specimens for definitive staging and grade analysis while also preserving the ipsilateral kidney.

- Ureteroureterostomy is indicated for non-invasive, low-grade tumours of the proximal ureter or mid-ureter that cannot be removed completely by endoscopic means (i.e. size or number) and for high-grade or invasive tumours when renal-sparing surgery for preservation of renal function is a goal (LE: 3).
- High-grade tumours of the proximal ureter or midureter should undergo RNU with excision of bladder cuff when possible. Complete distal ureterectomy and neocystostomy is indicated for non-invasive, low-grade tumours in the distal ureter that cannot be removed completely by endoscopic means (i.e. size or number) (118-120) (LE: 3)
- For both ureteroureterostomy and complete distal ureterectomy and neocystostomy, it is necessary to ensure there is no invasion of the area of tissue around the tumour.
- Segmental resection of the iliac and lumbar ureter is associated with a failure rate greater than that for the distal pelvic ureter (118-120).
- Open resection of tumours of the renal pelvis or calices has almost disappeared.
- Resection of pyelocaliceal tumours is technically difficult and the recurrence rate is higher than for ureteral tumours.

3.9.1.1.3 Percutaneous access

Percutaneous management can be considered for low-grade or non-invasive UTUCs in the renal cavities (114,121,122) (LE: 3). This treatment option may be offered to patients with low-grade tumours in the lower caliceal system that are inaccessible or difficult to manage by ureteroscopy. A theoretical risk of seeding exists in the puncture tract and in perforations that may occur during the procedure. However, this approach is being used less due to the availability of enhanced materials and advances in distal-tip deflection of recent ureteroscopes (114,121,122).

Table 4: Guidelines for conservative management of low-risk UTUC

Indications for conservative management of low-risk UTUC	**GR**
Unifocal tumour	B
Tumour size < 1 cm	B
Low-grade tumour (cytology or biopsies)	B
No evidence of an infiltrative lesion on CT urography	B
Understanding of close follow-up	B
Techniques used in conservative management of low-risk UTUC	
Laser should be used in case of endoscopic treatment	C
Flexible ureteroscopy is preferable over rigid ureteroscopy	C
A percutaneous approach remains an option in small low-grade caliceal tumours unsuitable for ureteroscopic treatment	C
Ureteroureterostomy is indicated for non-invasive low-grade tumours of the proximal ureter or mid-ureter that cannot be removed completely by endoscopic means	C
Complete distal ureterectomy and neocystostomy is indicated for non-invasive, low-grade tumours in the distal ureter that cannot be removed completely by endoscopic means and for high-grade, locally-invasive tumours	C

3.9.1.2 Adjuvant topical agents

The antegrade instillation of bacillus Calmette-Guérin (BCG) vaccine or mitomycin C in the upper urinary tract by percutaneous nephrostomy via a three-valve system open at 20 cm (after complete eradication of the tumour) is technically feasible after conservative treatment of UTUCs or for the treatment of CIS (123) (LE: 3). Retrograde instillation through a ureteric stent is also used for mitomycin and BCG but it can be dangerous due to possible ureteric obstruction and consecutive pyelovenous influx during instillation/perfusion. The reflux obtained from a double-J stent has also been used (124), but is not advisable since it often does not reach the renal pelvis.

3.9.2 ***High-risk UTUC***

3.9.2.1 Conservative surgery

Conservative management of high-risk UTUCs can be considered only in imperative cases (renal insufficiency or solitary functional kidney). Ureteroureterostomy is indicated for high-grade or invasive tumours when renal-sparing surgery for preservation of renal function is a goal.

3.9.2.2 Radical nephroureterectomy

Radical nephroureterectomy with excision of the bladder cuff is the gold standard treatment for high-risk UTUC, regardless of the tumour location in the upper urinary tract (14) (LE: 3). The RNU procedure must comply with oncological principles, which consist of preventing tumour seeding by avoiding entry into the urinary tract during tumour resection (14).

Resection of the distal ureter and its orifice is performed because this part of the urinary tract carries a considerable risk of tumour recurrence. After removal of the proximal part, it is almost impossible to image or approach it by endoscopy during follow-up. Recent publications on survival after RNU have concluded that removal of the distal ureter and bladder cuff is beneficial (110,125,126). **Regardless of the technique, the surgeon has to be confident that the bladder is closed appropriately.**

McDonald *et al*. presented the pluck technique in 1952, but it was not until 1995 (127) that the usefulness of an endoscopic approach to the distal ureter was emphasized. Several other techniques were then reconsidered to simplify resection of the distal ureter, including stripping, transurethral resection of the intramural ureter, and intussusception (11,126). Except for ureteral stripping, none of these techniques was inferior to excision of the bladder cuff (74-76,78) (LE: 3). However, the endoscopic approach is associated with a higher risk of subsequent bladder recurrence (128).

A delay between diagnosis and removal of the tumour may increase the risk of disease progression. However, the cut-off deadline for removal continues to be controversial and ranges between 45 days and 3 months (129-131) (LE: 3).

3.9.2.2.1 Lymph node dissection associated with RNU

Lymph node dissection (LND) associated with RNU is of therapeutic interest and allows for optimal staging of the disease (132,133) (LE: 3). However, the anatomical sites of LND have not yet been clearly defined. The LND template is likely to have a greater impact on patient survival than the number of lymph nodes removed (134).

Lymph node dissection appears to be unnecessary in cases of TaT1 UTUCs because lymph node retrieval has been reported in only 2.2% T1 versus 16% pT2-4 tumours (133). In addition, a continuous increase in the probability of lymph-node-positive disease related to pT classification has been described (133). However, as these data are retrospective, it is very likely that the true rate of node-positive disease has been under-reported. It is not yet possible to standardize either indication or extent of LND. However, LND can be achieved following lymphatic drainage as follows: LND medially to the ureter in ureteropelvic tumour, retroperitoneal LND in case of higher ureteral tumour and/or tumour of the renal pelvis (i.e. right side: border vena cava; and left side: border aorta) (132-134).

3.9.2.2.2 Laparoscopic RNU

Laparoscopic RNU has not yet achieved final proof of its safety. There are early reports of retroperitoneal metastatic dissemination and dissemination along the trocar pathway following the manipulation of large tumours in a pneumoperitoneal environment (135,136).

Several precautions must be taken when operating with a pneumoperitoneum because it may increase tumour spillage:

- Entering the urinary tract should be avoided;
- Direct contact of the instruments with the tumour should be avoided;
- Laparoscopic RNU must take place in a closed system. Morcellation of the tumour should be avoided and an endobag is necessary to extract the tumour;
- The kidney and ureter must be removed en bloc with the bladder cuff;
- Invasive or large (T3/T4 and/or N+/M+) tumours are contraindications for laparoscopic RNU until proven otherwise.

Recent data show a tendency towards equivalent oncological outcomes after either laparoscopic or open RNU (136-141). In addition, the laparoscopic approach appears to be superior to open surgery only with regard to functional outcomes (137-142) (LE: 3).

Only one prospective randomized study of 80 patients has provided evidence that laparoscopic RNU is not inferior to open RNU for non-invasive UTUC (143) (LE: 2). In addition, it has been demonstrated that oncological outcomes after RNU have not changed significantly over the past three decades despite staging and surgical refinements (144) (LE: 3).

3.9.2.3 Chemotherapy

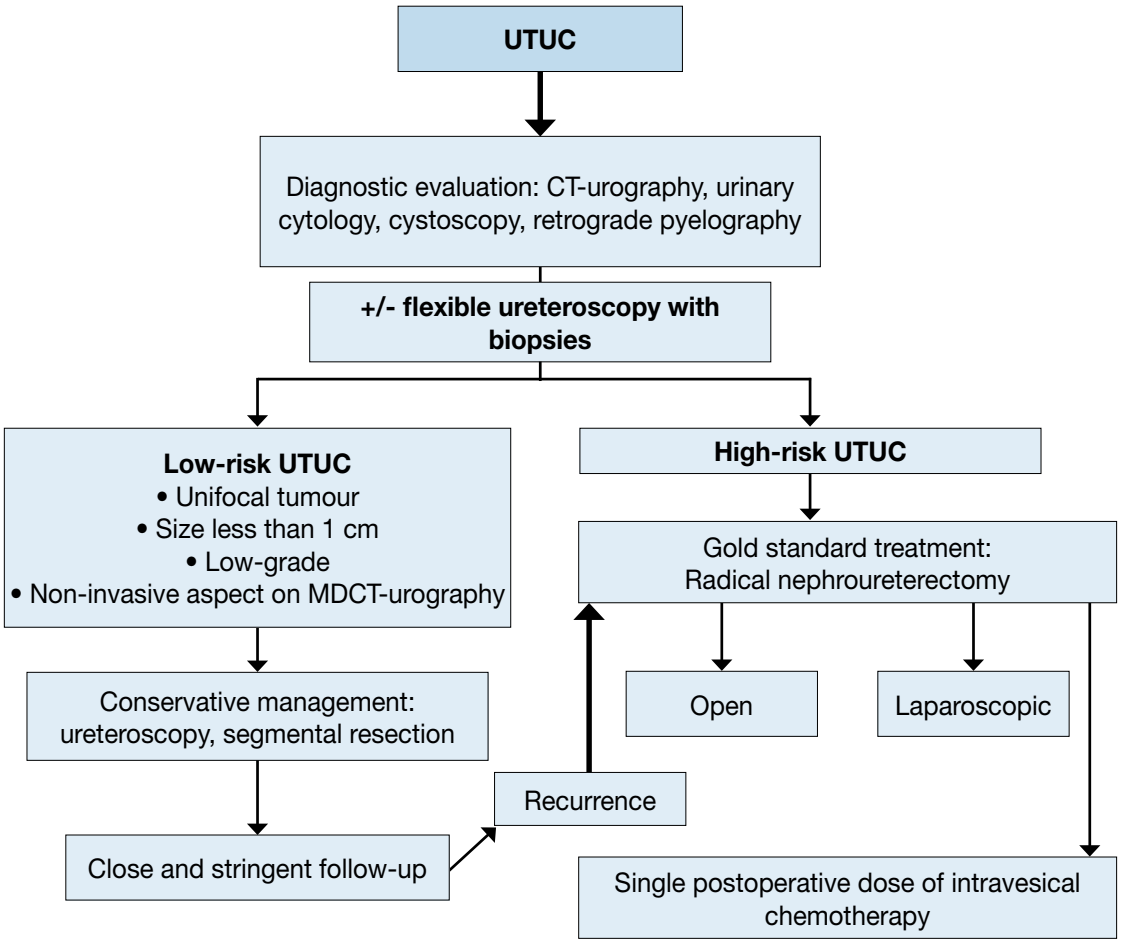
One prospective randomized study of 284 patients has provided evidence that a single post-operative dose of intravesical mitomycin administered on the day of catheter removal reduces the risk (i.e. absolute risk 11%) of a bladder tumour within the first year following RNU (145) (LE: 2). This therapeutic strategy was confirmed recently in another prospective trial with pirarubicin in 77 patients (146).

Recommendations are listed in Table 5 and a flow chart for the management is proposed in Figure 1.

Table 5: Guidelines for radical management of high-risk UTUC: radical nephroureterectomy (RNU)

Indications for RNU for UTUC	**GR**
Suspicion of infiltrating UTUC on imaging	B
High-grade tumour (urinary cytology)	B
Multifocality (with two functional kidneys)	B
Non-invasive but large (i.e. > 1 cm) UTUC	B
Techniques for RNU for UTUC	
Open and laparoscopic access are equivalent in terms of efficacy in T1-T2/N0 tumours	B
Bladder cuff removal is imperative	A
Several techniques for bladder cuff excision are acceptable, except stripping	C
Lymphadenectomy is recommended in cases of invasive UTUC	C
Post-operative instillation (chemotherapy) is recommended after RNU to avoid bladder recurrence	B

Fig. 1: Proposed flowchart for the management of UTUCs



CT-urography = computed tomography urography; MDCT-urography= multidetector-row computed tomography urography; UTUC = upper tract urothelial carcinoma

3.9.3 ***Advanced disease***

3.9.3.1 Radical nephroureterectomy

There are no benefits of RNU in metastatic (M+) disease, although it can be considered as a palliative option (14,133) (LE: 3).

3.9.3.2 Chemotherapy

Since UTUCs are urothelial tumours, platinum-based chemotherapy is expected to show similar results to those produced in bladder cancer. However, there are currently not enough data to provide any recommendations.

Several platinum-based chemotherapy regimens have been proposed (147), but the risk of impaired post-surgical function means that neoadjuvant chemotherapy is only an optional treatment. Not all patients can receive chemotherapy because of comorbidity and impaired renal function after radical surgery. Furthermore, the addition of chemotherapy-related toxicity, particularly nephrotoxicity from platinum derivatives, to a population with already impaired post-surgical renal function, may be significant in the reduced survival of these patients (148,149).

In contrast to research in bladder cancer, there were no reported effects of neoadjuvant chemotherapy for UTUCs in the only study published to date (150). Although survival data need to mature and longer follow-up is awaited, current preliminary data provide justification for the sustained support of trials using this strategy in UTUCs.

Adjuvant chemotherapy can somehow achieve a recurrence-free rate of up to 50%, but has clearly no impact on survival (151,152). Further data are awaited from the ongoing prospective randomized POUT trial (PeriOperative chemotherapy or sUrveillance in upper Tract urothelial cancer) (153).

3.9.3.3 Radiotherapy

Adjuvant radiotherapy may improve local control of the disease (154). When given in combination with cisplatin, it may result in longer disease-free and overall survival (155) (LE: 3). Radiotherapy appears to be scarcely relevant nowadays both as a unique therapy and associated with chemotherapy as adjuvant therapy.

3.10 Follow-up

Stringent follow-up of UTUC patients (Table 6) after surgical treatment is mandatory to detect metachronous bladder tumours (in all cases), local recurrence, and distant metastases (in the case of invasive tumours). When RNU is performed, local recurrence is rare and the risk of distant metastases is directly related to the risk factors listed previously. The reported recurrence rate within the bladder after treatment of a primary UTUC varies considerably from 22% to 47% (8,10). Thus, the bladder should be observed in all cases.

The surveillance regimen is based on cystoscopy and urinary cytology for at least 5 years (8-10). Bladder recurrence should not be considered as distant recurrence. When conservative treatment is performed, the ipsilateral upper urinary tract requires careful follow-up due to the high risk of recurrence (111,115,117). Despite notable improvements in endo-urological technology, the follow-up of patients treated with conservative therapy is difficult, and frequent and repeated endoscopic procedures are necessary.

Table 6: Guidelines for follow-up of UTUC patients after initial treatment

After RNU, over at least 5 years	**GR**
Non-invasive tumour	
Cystoscopy/urinary cytology at 3 months and then yearly	C
CT every year	C
Invasive tumour	
Cystoscopy/urinary cytology at 3 months and then yearly	C
CT urography every 6 months over 2 years and then yearly	C
After conservative management, over at least 5 years	
Urinary cytology and CT urography at 3 and 6 months, and then yearly	C
Cystoscopy, ureteroscopy and cytology *in situ* at 3 and 6 months, and then every 6 months over 2 years, and then yearly	C

4. CONCLUSIONS

These updated UTUC guidelines contain information for the diagnosis and treatment of individual patients according to a current, standardized approach. When determining the optimal treatment regimen for their patients, urologists must take into account each individual patient's specific clinical characteristics with regard to renal function, including medical comorbidity, tumour location, grade and stage, and molecular marker status.

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6. ABBREVIATIONS USED IN THE TEXT

This list is not comprehensive for the most common abbreviations

BCG	bacillus Calmette-Guérin
EBM	evidence-based medicine
CIS	carcinoma in situ
CT	computed tomography
EAU	European Association of Urology
EBM	evidence-based medicine
ECOG	Eastern Cooperative Oncology Group
FISH	fluorescence in situ hybridization
GR	grade of recommendation
HIF	hypoxia-inducible factor
HNPCC	hereditary non-polyposis colorectal carcinoma
LE	level of evidence
LND	lymph node dissection
MDCT	multidetector-row computed tomography
MR	magnetic resonance
MSI	microsatellite instability
RNU	radical nephroureterectomy
TNM	Tumour Node Metastasis
UICC	Union Internationale Contre le Cancer
UTUC	upper tract urothelial carcinoma
WHO	World Health Organization

Conflict of interest

All members of the Upper Urinary Tract Urothelial Carcinomas 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 publically accessible through the European Association of Urology website. This guidelines document was developed with the financial support of the European Association of Urology. No external sources of funding and support have been involved. The EAU is a non-profit organization, and funding is limited to administrative assistance and travel and meeting expenses. No honoraria or other reimbursements have been provided.