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DIAGNOSIS AND MANAGEMENT OF NON-METASTATIC UPPER TRACT UROTHELIAL CARCINOMA: AUA/SUO GUIDELINE (2023)

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SUMMARY

Purpose

The purpose of this guideline is to provide a useful reference on the effective evidence-based diagnoses and management of non-metastatic upper tract urothelial carcinoma (UTUC).

Methodology

The Pacific Northwest Evidence-based Practice Center of Oregon Health & Science University (OHSU) team conducted searches in Ovid MEDLINE (1946 to March 3rd, 2022), Cochrane Central Register of Controlled Trials (through January 2022), and Cochrane Database of Systematic Reviews (through January 2022). The searches were updated August 2022 and January 2023. When sufficient evidence existed, the body of evidence was assigned a strength rating of A (high), B (moderate), or C (low) for support of Strong, Moderate, or Conditional Recommendations. In the absence of sufficient evidence, additional information is provided as Clinical Principles and Expert Opinions.

GUIDELINE STATEMENTS

DIAGNOSIS AND EVALUATION

1. For patients with suspected UTUC, a cystoscopy and cross- sectional imaging of the upper tract with contrast including delayed images of the collecting system and ureter should be performed. (*Strong Recommendation; Evidence Level: Grade B*)

2. Clinicians should evaluate patients with suspected UTUC with diagnostic ureteroscopy and biopsy of any identified lesion and cytologic washing from the upper tract system being inspected. (*Strong Recommendation; Evidence Level: Grade C*)

3. In patients who have concomitant lower tract tumors (bladder/urethra) discovered at the time of ureteroscopy, the lower tract tumors should be managed in the same setting as ureteroscopy. (*Expert Opinion*)

4. In cases of existing ureteral strictures or difficult access to the upper tract, clinicians should minimize risk of ureteral injury by using gentle dilation techniques such as temporary stenting (pre-stenting) and limit use of aggressive dilation access techniques such as ureteral access sheaths. (*Expert Opinion*)

5. In cases where ureteroscopy cannot be safely performed or is not possible, an attempt at selective upper tract washing or barbotage for cytology may be made and pyeloureterography performed in cases where good quality imaging such as CT or MR urography cannot be obtained. (*Conditional Recommendation; Evidence Level: Grade C*)

6. At the time of ureteroscopy for suspected UTUC, clinicians should not perform ureteroscopic inspection of a radiographically and clinically normal contralateral upper tract. (*Expert Opinion*)

7. For patients with suspected/ diagnosed UTUC, clinicians should obtain a personal and family history to identify known hereditary risk factors for familial diseases associated with Lynch Syndrome (LS) (colorectal, ovarian, endometrial, gastric, biliary, small bowel, pancreatic, prostate, skin and brain cancer) for which referral for genetic counseling should be offered. (*Expert Opinion*)

8. Universal histologic testing of UTUC with additional studies, such as immunohistochemical (IHC) or microsatellite instability (MSI), should be performed to identify patients with high probability of Lynch-related cancers whom clinicians should refer for genetic counseling and germline testing. (*Strong Recommendation; Evidence Level: Grade B*)

RISK STRATIFICATION

9. At the time of identified UTUC, clinicians should perform a standardized assessment documenting clinically meaningful endoscopic (focality, location, appearance, size) and radiographic (invasion, obstruction, and lymphadenopathy) features to facilitate clinical staging and risk assessment. (*Strong Recommendation; Evidence Level: Grade B*)

10. Following standardized assessment, clinicians should risk-stratify patients as “low-” or “high” risk for invasive disease (pT2 or greater) based on obtained endoscopic, cytologic, pathologic, and radiographic findings. Further stratification into favorable and unfavorable risk groups should then be based on standard identified features (Table 5). (*Strong Recommendation; Evidence Level: Grade B*)

11. Patients with UTUC should be assessed prior to surgery for the risk of post-NU CKD or dialysis. (Expert Opinion)

TREATMENT

12. Clinicians should provide patients with a description of the short- and long-term risks associated with recommended diagnostic and therapeutic options. This includes the need for endoscopic follow-up, clinically significant strictures, toxicities associated with surgical treatment and side effects from neoadjuvant and adjuvant therapies. (*Clinical Principle*)

Kidney Sparing Management

13. Tumor ablation should be the initial management option for patients with LR favorable UTUC. (*Strong Recommendation; Evidence Level: Grade B*)

14. Tumor ablation may be the initial management option offered to patients with LR unfavorable UTUC and select patients with HR favorable disease who have low-volume tumors or cannot undergo RNU. (*Conditional Recommendation; Evidence Level: Grade C*)

15. Tumor ablation may be accomplished via a retrograde or antegrade percutaneous approach and repeat endoscopic evaluation should be performed within three months. (*Expert Opinion*)

16. Following ablation of UTUC tumors and after confirming there is no perforation of the bladder or upper tract, clinicians may instill adjuvant pelvicalyceal chemotherapy (*Conditional Recommendation; Evidence Level: Grade C*) or intravesical chemotherapy (*Expert Opinion*) to decrease the risk of urothelial cancer recurrence.

17. Pelvicalyceal therapy with BCG may be offered to patients with HR favorable UTUC after complete tumor ablation or patients with upper tract carcinoma in situ (CIS). (*Expert Opinion*)

18. When tumor ablation is not feasible or evidence of risk group progression is identified in patients with LR UTUC, surgical resection of all involved sites either by RNU or segmental resection of the ureter should be offered. (*Moderate Recommendation; Evidence Level: Grade C*)

19. Clinicians may offer watchful waiting or surveillance alone to select patients with UTUC with significant comorbidities, competing risks of mortality, or at significant risk of End-Stage Renal Disease (ESRD) with any intervention resulting in dialysis. (*Expert Opinion*)

Surgical Management

20. Clinicians should recommend RNU or SU for surgically eligible patients with HR UTUC. (*Strong Recommendation; Evidence Level: Grade B*)

21. For surgically eligible patients with HR and unfavorable LR cancers endoscopically confirmed as confined to the lower ureter in a functional renal unit, distal ureterectomy and ureteral reimplantation is the preferred treatment. (*Expert Opinion*)

22. When performing NU or distal ureterectomy, the entire distal ureter including the intramural ureteral tunnel and ureteral orifice should be excised, and the urinary tract should be closed in a watertight fashion. (*Strong Recommendation, Evidence Level: Grade B)*

23. In patients undergoing RNU or SU (including distal ureterectomy) for UTUC, a single dose of perioperative intravesical chemotherapy should be administered in eligible patients to reduce the risk of bladder recurrence. (*Strong Recommendation; Evidence Level: Grade A*)

Lymph Node Dissection (LND)

24. For patients with LR UTUC, clinicians may perform LND at time of NU or ureterectomy. (*Conditional Recommendation; Evidence Level: Grade C*)

25. For patients with HR UTUC, clinicians should perform LND at the time of NU or ureterectomy. (*Strong Recommendation; Evidence Level: Grade B)*

Neoadjuvant/Adjuvant Chemotherapy and Immunotherapy

26. Clinicians should offer cisplatin-based NAC to patients undergoing RNU or ureterectomy with HR UTUC, particularly in those patients whose post-operative eGFR is expected to be less than 60 mL/min/1.73m^2 or those with other medical comorbidities that would preclude platinum-based chemotherapy in the post-operative setting. (*Strong Recommendation; Evidence Level: Grade B*)

27. Clinicians should offer platinum-based adjuvant chemotherapy to patients with advanced pathological stage (pT2–T4 pN0–N3 M0 or pTany N1–3 M0) UTUC after RNU or ureterectomy who have not received neoadjuvant platinum-based therapy. (*Strong Recommendation; Evidence Level: Grade A*)

28. Adjuvant nivolumab therapy may be offered to patients who received neoadjuvant platinum-based chemotherapy (ypT2–T4 or ypN+) or who are ineligible for or refuse perioperative cisplatin (pT3, pT4a, or pN+). (*Conditional Recommendation; Evidence Level: Grade B*)

29. In patients with metastatic (M+) UTUC, RNU or ureterectomy should not be offered as initial therapy. (*Expert Opinion*)

30. Patients with clinical, regional node-positive (cN1-3, M0) UTUC should initially be treated with systemic therapy. Consolidative RNU or ureterectomy with lymph-node dissection may be performed in those with a partial or complete response. (*Expert Opinion*)

31. Patients with unresectable UTUC (including those who are ineligible or refuse surgery [RNU or ureterectomy]) should be offered a clinical trial or best supportive care including palliative management (radiation, systemic approach, endoscopic, or ablative) for refractory symptoms such as hematuria. (*Expert Opinion*)

SURVEILLANCE AND SURVIVORSHIP

Post-Treatment Surveillance

Surveillance After Kidney Sparing

32. Low-risk patients managed with kidney sparing treatment should undergo a follow-up cystoscopy and upper tract endoscopy within one to three months to confirm successful treatment. Once confirmed, these patients should undergo continued cystoscopic surveillance of the bladder at least every six to nine months for the first two years and then at least annually thereafter. Endoscopy should be repeated at six months and one year. Upper tract imaging should be performed at least every six to nine months for two years, then annually up to five years. surveillance after five years in the absence of recurrence should be based on shared decision-making between the patient and clinician. (*Expert Opinion*)

33. High-risk patients managed with kidney sparing treatment should undergo a follow-up cystoscopy and upper tract endoscopy with cytology within one to three months. Patients with no evidence of disease should undergo cystoscopic surveillance of the bladder and cytology at least every three to six months for the first three years and then at least annually thereafter. Endoscopy should be repeated at least at six months and one year. Upper tract imaging should be performed every three to six months for three years, then annually up to five years. surveillance after five years in the absence of recurrence should be encouraged and based on shared decision-making between the patient and clinician. (*Expert Opinion*)

34. Patients who develop urothelial recurrence in the bladder or urethra or positive cytology following treatment for UTUC should be evaluated for possible ipsilateral recurrence or development of new contralateral upper tract disease. (*Expert Opinion*)

Surveillance after Radical NU

35. After NU, patients with <pT2 N0/M0 disease should undergo surveillance with cystoscopy and cytology within three months after surgery, then repeated based on pathologic grade. For LG this should repeated at least every six to nine months for the first two years and then at least annually thereafter. For HG, this should be repeated at least every three to six months for the first three years and then at least annually thereafter. Due to the metastasis risk and estimated 5% probability for contralateral disease, cross-sectional imaging of the abdomen and pelvis should

be done within 6 months after surgery and then at least annually for a minimum of 5 years. Surveillance after five years in the absence of recurrence should be encouraged and based on shared decision-making between the patient and clinician (See Table 6). *(Expert Opinion*)

T2+ MANAGED WITH NU

36. For Patients who have undergone NU for ≥pT2 Nx/0 disease, a clinician should perform surveillance cystoscopy with cytology at three months after surgery, then every three to six months for 3 years, and then annually thereafter. Cross-sectional imaging of the abdomen and pelvis with multiphasic contrast-enhanced CT urography should be performed every three to six months for years one and two, every six months at year three, and annually thereafter to year five. A clinician should perform chest imaging, preferably with chest CT, every 6-12 months for the first 5 years. Beyond five years after surgery in patients without recurrence, ongoing surveillance with cystoscopy and upper tract imaging may be continued on an annual basis according to principles of shared/informed decision-making. (*Expert Opinion*)

Survivorship

37. For patients with reduced or deteriorating renal function following NU or other intervention, clinicians should consider referral to nephrology. (*Expert Opinion*)
38. Clinicians should discuss disease-related stresses and risk factors and encourage patients with urothelial cancer to adopt healthy lifestyle habits, including smoking cessation, exercise, and a healthy diet, to promote long-term health benefits and quality of life. (*Expert Opinion*)

INTRODUCTION

PURPOSE

Upper Tract urothelial cancer (UTUC) is a rare disease, posing unique challenges to clinical management and significant risks to patients – both from the disease and treatment forms. UTUC is often considered analogous to urothelial cancer of the bladder, yet pathogenic, genomic, biologic, and clinical distinctions between these entities have been identified.[1, 2] As a clinically clear example, the diagnosis of UTUC of the renal pelvis is associated with a 5-year mortality rate >50%, comparatively worse than the <25% rate for bladder cancer.[3] The risk of renal functional loss and associated patient morbidity places patients at an additional clinical disadvantage, warranting specialized approaches and instrumentation for disease assessment, clinical staging and management. Such aspects highlight the clear need for well-designed, multi-disciplinary strategies to guide optimal management for this vulnerable patient population to control variability and reduce the risks from under- and over-treatment. Emerging data from standardized paradigms for evaluation, counseling, and management provide a basis for appropriate risk stratified approaches to optimize patient care, limit toxicity, and improve cancer control and survival. Curation and dissemination of this information, especially in a rare disease prone to clinical complexity, is critical to well-informed patient care and the consideration for referral to experienced, multi-disciplinary teams in more challenging cases.

METHODOLOGY

Panel Formation and Process

The UTUC Panel was created in 2021 by the American Urological Association Education and Research, Inc. (AUAER) to develop a clinical guideline addressing management of localized or regionally advanced UTUC. This guideline was developed in collaboration with the Society of Urologic Oncology (SUO). The Practice Guidelines Committee (PGC) of the AUA selected the Panel Chair who in turn appointed the additional panel members based on an open nomination process. The Panel included specialists from urology and oncology.

Search Strategy

The Pacific Northwest Evidence-based Practice Center of Oregon Health & Science University (OHSU) team conducted searches in Ovid MEDLINE (1946 to March 3rd, 2022), Cochrane Central Register of Controlled Trials (through January 2022), and Cochrane Database of Systematic Reviews (through January 2022). The searches were updated August 2022 and January 2023. The team developed a search strategy by using medical subject headings terms and key words relevant to the diagnosis and treatment UTUC. The evidence review team also reviewed relevant systematic reviews and references provided by the Panel to identify articles that may have been missed by the database searches.

Study Selection and Data Abstraction

Study selection was based on predefined eligibility criteria for the patient populations, interventions, outcomes, and study designs of interest. Two reviewers independently screened titles, abstracts, and full text for inclusion. Differences between reviewers regarding eligibility were resolved through consensus.

Assessment of Risk of Bias (ROB) of Individual Studies

Two investigators independently assessed ROB using predefined criteria. Disagreements were resolved by consensus. For randomized trials and cohort studies, criteria for assessing ROB were adapted from the U.S. Preventive Services Task Force.[4] Criteria for randomized trials included use of appropriate randomization and allocation concealment methods, baseline comparability of groups, blinding, attrition, and use of intention-to-treat analysis. For cohort studies on prognostic factors, criteria included methods for assembling cohorts, attrition, blinding assessment of outcomes, and adjustment for potential confounding. Systematic reviews were assessed using AMSTAR 2 (Assessing the Methodological Quality of Systematic Reviews) criteria. [5] Criteria included use of pre-specified methods, appropriate search methods, assessment of risk of bias, and appropriate synthesis methods. Studies were rated as “low ROB,” “moderate ROB,” or “high ROB” based on the presence and seriousness of methodological

shortcomings. The evidence review team graded strength of evidence on outcomes by adapting the AUA's three predefined levels (A, B, or C) of strength of evidence.

Determination of Evidence Strength

The categorization of evidence strength is conceptually distinct from the quality of individual studies. Evidence strength refers to the body of evidence available for a particular question and includes not only the quality of individual studies but consideration of study design; consistency of findings across studies; adequacy of sample sizes; and generalizability of study populations, settings, and interventions for the purposes of the guideline. The AUA categorizes body of evidence strength as Grade A (well-conducted and highly-generalizable randomized control trial (RCTs) or exceptionally strong observational studies with consistent findings), Grade B (RCTs with some weaknesses of procedure or generalizability or moderately strong observational studies with consistent findings), or Grade C (RCTs with serious deficiencies of procedure or generalizability or extremely small sample sizes or observational studies that are inconsistent, have small sample sizes, or have other problems that potentially confound interpretation of data). By definition, Grade A evidence has a high level of certainty, Grade B evidence has a moderate level of certainty, and Grade C evidence has a low level of certainty **(Table 1)**.[6]

Table 1: Strength of Evidence Definitions

AUA Strength of Evidence Category	GRADE Certainty Rating	Definition
A	High	• Very confident that the true effect lies close to that of the estimate of the effect
B	Moderate	• Moderately confident in the effect estimate • The true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different
C	Low	• Confidence in the effect estimate is limited • The true effect may be substantially different from the estimate of the effect
	Very Low	• Very little confidence in the effect estimate • The true effect is likely to be substantially different from the estimate of effect

AUA Nomenclature: Linking Statement Type to Evidence Strength

The AUA nomenclature system explicitly links statement type to body of evidence strength, level of certainty, magnitude of benefit or risk/burdens, and the Panel's judgment regarding the balance between benefits and risks/burdens **(Table 2)**. ***Strong Recommendations*** are directive statements that an action should (benefits outweigh risks/burdens) or should not (risks/burdens outweigh benefits) be undertaken because net benefit or net harm is substantial. ***Moderate Recommendations*** are directive statements that an action should (benefits outweigh risks/burdens) or should not (risks/burdens outweigh benefits) be undertaken because net benefit or net harm is moderate. ***Conditional Recommendations*** are non-directive statements used when the evidence indicates there is no apparent net benefit or harm or when the balance between benefits and risks/burden is unclear. All three statement types may be supported by any body of evidence strength grade. Body of evidence strength Grade A in support of a Strong or Moderate Recommendation indicates the statement can be applied to most patients in most circumstances and that future research is *unlikely to change confidence*. Body of evidence strength Grade B in support of a Strong or

Moderate Recommendation indicates the statement can be applied to most patients in most circumstances, but better evidence *could change confidence*. Body of evidence strength Grade C in support of a Strong or Moderate Recommendation indicates the statement can be applied to most patients in most circumstances, but better evidence is *likely to change confidence*. Body of evidence strength Grade C is only rarely used in support of a Strong Recommendation. Conditional Recommendations can also be supported by any evidence strength. When body of evidence strength is Grade A, the statement indicates benefits and risks/burdens appear balanced, the best action depends on patient circumstances, and future research is *unlikely to change confidence*. When body of evidence strength Grade B is used, benefits and risks/burdens appear balanced, the best action also depends on individual patient circumstances, and better evidence *could change confidence*. When body of evidence strength Grade C is used, there is uncertainty regarding the balance between benefits and risks/burdens, alternative strategies may be equally reasonable, and better evidence is *likely to change confidence*.

Where gaps in the evidence existed, Clinical Principles or Expert Opinions are provided via consensus of the Panel. A **Clinical Principle** is a statement about a component of clinical care widely agreed upon by urologists or other clinicians for which there may or may not be evidence in the medical literature. **Expert Opinion** refers to a statement based on members' clinical training, experience, knowledge, and judgment for which there may or may not be evidence in the medical literature.

Peer Review and Document Approval

An integral part of the guideline development process at the AUA is external peer review. The AUA conducted a thorough peer review process to ensure that the document was reviewed by experts in the diagnosis and treatment of UTUC. In addition to reviewers from the AUA PGC, Science and Quality Council (SQC), and Board of Directors (BOD), the document was reviewed by representatives from the American Society of Clinical Oncology (ASCO), American Society for Radiation Oncology (ASTRO), and SUO as well as external content experts. Additionally, a call for reviewers was placed on the AUA website from November 18- December 2, 2022, to allow any additional interested parties to request a copy of the document for review. The guideline was also sent to the Urology Care Foundation and the AUA Public Policy & Advocacy team to open the document further to the patient perspective. The draft guideline document was distributed to 114 peer reviewers. All peer review comments were blinded and sent to the Panel for review. In total, 46 reviewers provided comments, including 34 external reviewers. At the end of the peer review process, a total of 681 comments were received. Following comment discussion, the Panel revised the draft as needed. Once finalized, the guideline was submitted for approval to the AUA PGC, SQC, and BOD for final approval.

BACKGROUND

UTUC refers to urothelial tumors that originate from the inner lining of the ureter, calyces, or renal pelvis.[7] These anatomic structures derive embryologically from mesoderm and the ureteric bud associated with the wolffian duct, separate and distinct from the bladder and urethra, which are endodermal structures developed from the cloaca. Although related in pathogenesis to lower tract urothelial cancer (bladder and urethra), UTUC is much less common, only affecting 5-10% of all patients with urothelial carcinoma though poorly documented such that true estimates of incidence are difficult to track.[8] According to the American Cancer Society, approximately 4,010 Americans will be diagnosed with cancer of the ureter/other urinary organs in 2022. Surveillance, Epidemiology, and End Results (SEER) estimates report a consistent incidence of renal pelvic tumors between 0.9 - 1.0 cases per 100,000 in the U.S. through 2019, equaling between 2,980-3,280 cases per year.[7] Together, these data indicate an estimated total incidence of UTUC of just over 7,000 U.S. cases per year – slightly less than the annual incidence of testis cancer (8,000 – 10,000 cases).

As a rare disease with complex management paradigms, clinicians should have knowledge of patient demographics, staging distribution and causative factors when evaluating patients with suspected UTUC. According to SEER population data, approximately 25% of cases will present as localized disease, over 50% will have regionally advanced cancers, and nearly 20% will have distant disease at the time of diagnosis. Peak incidence is seen in adults aged >70 years and is three times more common in men than women in western

countries.[3, 9] Risk factors include occupational exposure, geographic location, Balkan endemic nephropathy associated with aristolochia herbal ingestion, chronic upper tract inflammation, and hereditary factors such as Lynch and Lynch-like syndromes.[10]

Table 2: AUA Nomenclature Linking Statement Type to Level of Certainty, Magnitude of Benefit or Risk/Burden, and Body of Evidence Strength

Evidence Grade	Evidence Strength A (High Certainty)	Evidence Strength B (Moderate Certainty)	Evidence Strength C (Low Certainty)
Strong Recommendation (Net benefit or harm substantial)	-Benefits > Risks/Burdens (or vice versa) -Net benefit (or net harm) is substantial -Applies to most patients in most circumstances and future research is unlikely to change confidence	-Benefits > Risks/Burdens (or vice versa) -Net benefit (or net harm) is substantial -Applies to most patients in most circumstances but better evidence could change confidence	-Benefits > Risks/Burdens (or vice versa) -Net benefit (or net harm) appears substantial -Applies to most patients in most circumstances but better evidence is likely to change confidence (rarely used to support a Strong Recommendation)
Moderate Recommendation (Net benefit or harm moderate)	-Benefits > Risks/Burdens (or vice versa) -Net benefit (or net harm) is moderate -Applies to most patients in most circumstances and future research is unlikely to change confidence	-Benefits > Risks/Burdens (or vice versa) -Net benefit (or net harm) is moderate -Applies to most patients in most circumstances but better evidence could change confidence	-Benefits > Risks/Burdens (or vice versa) -Net benefit (or net harm) appears moderate -Applies to most patients in most circumstances but better evidence is likely to change confidence
Conditional Recommendation (Net benefit or harm comparable to other options)	-Benefits = Risks/Burdens -Best action depends on individual patient circumstances -Future Research is unlikely to change confidence	-Benefits = Risks/Burdens -Best action appears to depend on individual patient circumstances -Better evidence could change confidence	-Balance between Benefits & Risks/Burdens unclear -Net benefit (or net harm) comparable to other options -Alternative strategies may be equally reasonable -Better evidence likely to change confidence
Clinical Principle	a statement about a component of clinical care that is widely agreed upon by urologists or other clinicians for which there may or may not be evidence in the medical literature		
Expert Opinion	a statement, achieved by consensus of the Panel, that is based on members' clinical training, experience, knowledge, and judgment for which there may or may not be evidence in the medical literature		

Guideline Statements

DIAGNOSIS AND EVALUATION

1. **For patients with suspected UTUC, a cystoscopy and cross- sectional imaging of the upper tract with contrast including delayed images of the collecting system and ureter should be performed. (*Strong Recommendation; Evidence Level: Grade B*)**

Cystoscopy is an essential component of the evaluation for patients with suspected UTUC due to the risk of concurrent lower tract urothelial cancer in this population.

If there are no contraindications to its use, clinicians should perform a multiphase computed tomography (CT) scan with excretory phase imaging of the urothelium. A systematic review by Janisch et al. highlighted that CT urography was associated with a pooled sensitivity of 92% (95% CI: 85% to 96%), pooled specificity of 95% (95% CI: 88% to 98%), and a summary area under the ROC curve of 0.97 (95% CI: 0.96 to 0.98)[11] using histopathology or a negative clinical follow-up as referent standard. Two additional studies published after the systematic review reported results consistent with this review.[12, 13]

In patients with contraindications to contrast-enhanced CT such as chronic kidney disease (CKD) or untreatable allergy to iodinated contrast medium, clinicians may utilize magnetic resonance (MR) urography. In a study of 88 patients, Takahashi et al. found MR urography was associated with a per-patient sensitivity of 63% to 74% and specificity of 96% to 97% for diagnoses of UTUC.[14]

For patients with contraindications to multiphasic CT and MR urography, clinicians may utilize retrograde pyelography in conjunction with non-contrast axial imaging to assess the upper urinary tracts. Renal ultrasound (US) may also have utility in providing additional diagnostic assessment. In a study of 151 imaged urinary tracts, retrograde pyelography was associated with a per-tract diagnostic sensitivity of 96%, specificity of 97%, positive predictive value (PPV) of 87%, and negative predictive value (NPV) of 97%[15] with referent standard of histopathology (biopsy or final surgical pathology) and clinical follow-up for 3-5 years. While no reports have specifically evaluated the diagnostic accuracy of US for UTUC alone, one study of 575 patients evaluated the accuracy of US (followed by CT only if US was suspicious) for the diagnosis of upper urinary tract malignancies (renal cell carcinoma or UTUC) in a population with hematuria.[13] In this cohort, US was associated with high sensitivity (100%) and specificity (97%) for upper tract malignancies, with a PPV of 18% and NPV of 100% with referent standard being histopathology from biopsy or radical nephroureterectomy (RNU). An important caveat is that renal cell carcinoma accounted for two-thirds of the cases in this series and that the study was not structured as a head-to-head comparison of US and CT.[13] Recognizing these limitations, the Panel cannot recommend the routine use of renal sonography for evaluating patients with suspected UTUC though recognizes there may be clinical utility in the narrow indications where contrast-based CT and MRI studies cannot be performed.

2. **Clinicians should evaluate patients with suspected UTUC with diagnostic ureteroscopy and biopsy of any identified lesion and cytologic washing from the upper tract system being inspected. (*Strong Recommendation; Evidence Level: Grade C*)**

After initial concerns of UTUC are discovered on imaging, endoscopy by antegrade or retrograde approach with tissue sampling and cytologic washing should be performed when diagnostic and prognostic details are needed. When performed, this diagnostic procedure should be performed as a standardized endoscopic examination including elements pertinent to clinical decision-making. At ureteroscopic evaluation, clinicians should document key descriptive features of UTUC including tumor size, number, location, focality, and appearance. These factors may guide further diagnostic testing and inform therapeutic interventions as well as provide points of comparison for subsequent ureteroscopic surveillance. An example checklist for standardized endoscopic diagnostic examination is provided in **Table 3**. The Panel recognizes and emphasizes a distinction between diagnostic and therapeutic endoscopic procedures for UTUC. Diagnostic procedures are intended as low-impact and typically brief interventions to provide clinical information required for risk-adapted patient care whereas therapeutic endoscopic procedures are often longer, more technically involved operations undertaken with curative intent and

greater risk for surgical complications. Under either circumstance, it is recommended that standardized reporting of findings be documented. Diagnostic and therapeutic procedures may overlap under circumstances where discovered tumors are small and can be easily and completely treated at the time of endoscopy. It is further recognized that endoscopic procedures carry risks including perforation and tumor seeding, inside and outside the urinary tract,that may complicate future management. Data on the comparative risks of retrograde vs antegrade percutaneous approaches are insufficient to address the concern regarding potential risk of tumor seeding with percutaneous techniques.

Different techniques exist for endoscopic approach including retrograde ureteroscopy versus antegrade percutaneous nephroscopy and/or ureteroscopy. Both approaches allow visualization of suspected lesions, and a variety of biopsy techniques can subsequently be employed which can successfully yield tissue adequate for diagnosis. Factors such as tumor location, configuration, size, and patient factors (e.g., prior cystectomy) may influence the chosen approach or technique. Data on comparative effectiveness across all clinical situations are lacking.

Six studies evaluated the diagnostic accuracy of endoscopic (ureteroscopic) biopsy for UTUC, compared against a reference standard of surgical pathology (e.g., following nephroureterectomy [NU]) or surgical pathology plus clinical follow-up.[16-21] One study (n=93 patients with 118 biopsies) found ureteroscopic biopsy with forceps was associated with diagnostic sensitivity of 83% and specificity of 100%.[18] Another study (n=45) reported fluoroscopically guided retrograde brush biopsy was associated with diagnostic sensitivity of 91% and specificity of 88% for UTUC.[21] Additional details of biopsy and cytology sampling accuracy are provided in Appendix I. Although the sensitivity and specificity of biopsy by forceps or loop for yielding a diagnosis of UTUC may be higher than brush biopsy and/or fine-needle aspiration (FNA) and thus be preferred, patient and tumor characteristics will likely dictate the optimal biopsy technique. Mucosal abnormalities may be difficult to biopsy effectively and thus attempted tissue confirmation may be facilitated with the use of brush biopsies or percutaneous image-guided biopsy.

The Panel recognizes there are rare situations where endoscopic upper tract evaluation may not be necessary, when other diagnostic means clearly confirm the diagnosis of UTUC and thus histologic tissue confirmation is not clinically required. Such scenarios may include those patients with high-grade (HG) selective cytology or other source of tissue diagnosis, and clear and convincing radiographic findings of upper tract urothelial-based tumor(s) such as patients with an obvious enhancing, urothelial based soft-tissue filling defect on contrast-enhanced imaging with urography. Such situations may be particularly relevant in patients with a history of HG urothelial cancer. Other clinically justifiable scenarios for omitting diagnostic endoscopic evaluation may occur when findings would not influence decision-making, such as patients with severe co-morbidities who are ineligible for intervention or request expectant management. In such cases it is recommended that documentation of clinical rationale is provided.

Urine cytology can be helpful in identifying carcinoma in the upper tracts. Adjunctive cytologic barbotage washing with saline obtained from selective ipsilateral collection prior to use of any contrast is preferred to a voided urinary specimen due to improved cellular yield, to avoid potential contamination in case of concomitant bladder and/or prostatic urethral disease as well as theoretical dilution of the specimen from a normal contralateral unit, all of which further reduce sensitivity.[22] Urine cytology classification has been standardized under The Paris System, which prioritizes the identification of HG cells while minimizing the ambiguity of non-HG findings. By this convention, urine cytology is reported according to seven categories: nondiagnostic, negative for HG urothelial carcinoma (NHGUC), atypical urothelial cells (AUC), suspicious for HG urothelial carcinoma (SHGUC), HGUC, low-grade (LG) urothelial neoplasm (LGUN), and other malignancies.[23] Adoption of The Paris System began in 2016, taking time to become more widely accepted, and thus may impact interpretation of studies with data obtained prior to use of this standard.

Urine fluorescence in situ hybridization (FISH) testing may also be helpful in the diagnosis of UTUC. One previously described systematic review[24] including 14 studies (N=2,031) found that FISH was associated with high diagnostic accuracy for identifying UTUC with a pooled sensitivity of 84% (95% CI: 74% to 90%; range: 52% to 100%) and a pooled specificity of 90% (95% CI:

85% to 93%; range: 33% to 96%). The pooled positive and negative likelihood ratios were 7.96 (95% CI: 5.87 to 10.81) and 0.18 (95% CI: 0.11 to 0.29), respectively. Based on the head-to-head comparisons in the review, sensitivity of FISH was higher than for voided urine cytology, with similar specificity. However, use was not evaluated for selective, instrument-obtained samples from the suspected upper tract. Analogous to cytology, selective collection from the suspected renal and/or ureteral unit likely improves performance characteristics. Given the high sensitivity and low specificity of FISH compared to voided cytology, the Panel acknowledges the yet uncertain role of FISH and suggests such testing may be considered adjunctively to adjudicate atypical or suspicious cytology results.

3. **In patients who have concomitant lower tract tumors (bladder/urethra) discovered at the time of ureteroscopy, the lower tract tumors should be managed in the same setting as ureteroscopy. (*Expert Opinion*)**

A common clinical scenario when managing patients with UTUC, the finding of urothelial tumors in the lower tract (bladder or urethra) warrants appropriate independent guideline-directed management in the same surgical setting by biopsy, resection or ablation as clinically indicated. This feature of UTUC has been described clinically and further investigated through genomic studies, which show clonal similarity between upper and

Table 3: Standardized Upper Tract Endoscopy Suggested Reporting Elements

Elements		Reporting			
Approach		□ Antegrade	□ Retrograde		
		Access Details:			
Bladder Lesions		□ No	□ Yes		
		If yes, Details:			
Ureteral Lesions		□ No	□ Yes		
	If Yes, Location:	□ Lower	□ Mid	□ Upper	
	Appearance	□ Papillary	□ Sessile	□ Flat	□ Other:
	Focality	□ Unifocal	□ Multifocal		
	Largest Size	_____mm	Visual Reference:		
	Obstruction	□ No	□ Yes		
	Biopsied	□ No	□ Yes		
		If yes, Details:			
	Cytology	□ No	□ Yes		
Renal Pelvis / Calyceal Lesions		□ No	□ Yes		
	If Yes, Location:	□ Upper Calyx	□ Mid Calyx	□ Lower Calyx	□ Pelvis
	Appearance	□ Papillary	□ Sessile	□ Flat	□ Other:
	Focality	□ Unifocal	□ Multifocal		
	Largest Size	_____mm	Visual Reference:		
	Obstruction	□ No	□ Yes		
	Biopsied	□ No	□ Yes		
		If yes, Details:			
	Cytology	□ No	□ Yes		
Ancillary Tests	Bladder Cytology	□ No	□ Yes		
	Upper Tract Washing	□ No	□ Yes		
	Uretero-Pyelogram	□ No	□ Yes	Details:	
	Cystogram	□ No	□ Yes	Details:	
	Other:				
Visualization Quality		□ Good	□ Limited	□ Poor	
Comments	Observations:				

lower tract tumors, suggesting either downstream or upstream tumor implantation as a potential mechanism. The pathology findings from bladder tumor sampling often reflects that of upper tract tumors, though not reliably enough to be used as rationale for avoiding separate upper tract endoscopy and biopsy when feasible.[2, 25]

Consensus on prioritization of procedure sequencing (managing bladder before or after same-setting ureteroscopy) is lacking and heavily scenario-dependent. Rationale for managing the bladder first include optimizing visualization within the bladder, avoiding back-pressure or back-washing into the upper tract in the case of post-ureteroscopy stenting, and permitting final confirmation of bladder hemostasis. Addressing the upper tract first may be preferred in cases of bulky bladder tumor involvement where complete resection is not possible or bulky upper tract disease in which risk assessment is the priority. Seeding of tumors from bladder to upper tract or from upper tract to the lower tract have been raised as legitimate concerns which some have addressed by advocating use of ureteral access sheaths in such circumstances, yet the benefits of this approach require further prospective study.

4. **In cases of existing ureteral strictures or difficult access to the upper tract, clinicians should minimize risk of ureteral injury by using gentle dilation techniques such as temporary stenting (pre-stenting) and limit use of aggressive dilation access techniques such as ureteral access sheaths. (*Expert Opinion*)**

Perforation or disruption of the urothelium in patients with UTUC can risk tumor seeding outside the urinary tract. Precautionary measures in cases of difficult ureteral access such as avoiding dilation or placing a stent without performing ureteroscopy and then returning one-two weeks later to repeat the procedure (pre-stenting) can decrease the risk of iatrogenic injury and provide opportunity for a safer and more successful procedure. Recognized perforation or injury events should be documented with immediate cessation of the procedure as soon as safely possible with additional steps to limit sequelae (e.g., stenting, bladder decompression with urethral catheter drainage to limit reflux, nephrostomy tube placement in cases of a completely obstructive ureteral tumor and evidence of contrast extravasation).

5. **In cases where ureteroscopy cannot be safely performed or is not possible, an attempt at selective upper tract washing or barbotage for cytology may be made and pyeloureterography performed in cases where good quality imaging such as CT or MR urography cannot be obtained. (*Conditional Recommendation; Evidence Level: Grade C*)**

Findings from selective cytology and retrograde pyelography may provide useful, objective and sufficient information for risk stratification when endoscopic examination of the involved upper tract is not possible.[22] Example scenarios may include washings taken at the time of percutaneous nephrostomy tube placement or during attempted retrograde ureteroscopy that is abandoned for safety concerns. Cytologic sampling from the upper urinary tract, either by barbotage (irrigation and aspiration) or by irrigation with passive collection (washings) can be used to improve cellular yield for cytologic evaluation and best performed prior to pyelography to avoid artifactual cellular changes from contrast solutions. The Panel recognizes that this approach is supported by evidence associated with Statement 2 above and felt that guidance on this scenario was warranted as a Conditional Recommendation to describe means for risk-directed patient care in the setting of limited data from endoscopy, biopsy, and imaging.

6. **At the time of ureteroscopy for suspected UTUC, clinicians should not perform ureteroscopic inspection of a radiographically and clinically normal contralateral upper tract. (*Expert Opinion*)**

Indications for ureteroscopy or percutaneous endoscopy of the upper urinary tract include such findings as lateralizing hematuria, suspicious selective cytology, and radiographic presence of a mass or urothelial thickening. Endoscopic procedures have risks for patient injury and the potential for tumor seeding in the presence of urothelial cancer. Performing upper tract endoscopy in the setting of a completely normal contralateral upper urinary tract without clinical indication or as a “screening” procedure is unnecessary, placing patients at undue risk and should not be performed.

7. **For patients with suspected/ diagnosed UTUC, clinicians should obtain a personal and family history to identify known hereditary risk factors for familial diseases associated with Lynch Syndrome (LS) (colorectal, ovarian, endometrial, gastric, biliary, small bowel, pancreatic, prostate, skin and brain cancer) for which referral for genetic counseling should be offered. (*Expert Opinion)***

The significant role of hereditary risk factors in numerous malignancies is well recognized and a topic that care providers must be familiar and comfortable discussing with patients.

LS is common among patients with UTUC, accounting for an estimated 7-20% of U.S. cases. However, LS is frequently unrecognized as a risk factor in this setting and warrants specific attention during clinical assessment. Routine evaluation should include a detailed personal and family history to ask about specific LS associated cancers to clinically identify at-risk patients and their family members.

LS is a familial, autosomal-dominant multi-organ cancer syndrome estimated to affect roughly 1 in 280 individuals in the U.S.[26] It is widely and strongly recommended (e.g., ASCO, National Comprehensive Cancer Network [NCCN], Centers for Disease Control and Prevention [CDC]) that patients with LS undergo routine screening due to increased life-long risk for developing associated malignancies, often occurring before 50 years of age, though not exclusively.[27] The most commonly encountered are colorectal (20-80%), urothelial (1-18%), and gastric cancers (1-13%) in both men and women; and endometrial (15-60%) and ovarian cancer (1-38%) in women. Practice guidelines by several organizations (e.g., US Multi-Society Task Force on Colorectal Cancer [MSTF], ASCO, European Society of Medical Oncology [ESMO], NCCN, American College of Gastroenterology [ACG], American College of Obstetrics and Gynecology [ACOG]) recommend routine clinical screening including the use of standardized genomic questionnaires for all patients with related gastrointestinal (colon, gastric) and gynecologic (endometrial, ovarian) cancers.

Competing LS-associated cancers or related suspicious findings can pose potential clinical challenges requiring involvement and coordination of multi-disciplinary care. In UTUC specifically, LS may increase the possibility of contralateral upper tract involvement, which is an important potential clinical consideration when developing a treatment plan. The Panel notes that developing data on systemic therapies focused on targeting LS-associated cancers are expected to impact future therapeutic options for these patients, further reinforcing the overlap between genetic risk factors and need for alignment with clinical guidelines for preventative and therapeutic management of UTUC in patients with LS.

For UTUC patients with familial risk factors, clinical suspicion, or interest in further testing for hereditary syndromes, clinicians can perform initial screening tests (described below), and should offer referral for genetic counseling and, if indicated, genetic testing.

8. **Universal histologic testing of UTUC with additional studies, such as immunohistochemical (IHC) or microsatellite instability (MSI), should be performed to identify patients with high probability of Lynch-related cancers whom clinicians should refer for genetic counseling and germline testing. (*Strong Recommendation; Evidence Level: Grade B*)**

Clinical screening criteria including standard Amsterdam II criteria and Bethesda guidelines **(Table 4)** are useful in providing background context yet are unreliable, difficult to implement, and fail to identify a significant proportion of patients with LS or sufficiently exclude patients from screening.[28] Routine tissue testing provides a more sensitive, first-line means to identify LS-associated features in tumor samples, thus providing clinically significant information for patient counseling and management as well as screening for family members. IHC testing for example, which is widely available, can preliminarily identify the altered proteins associated with LS, and thus help to identify patients who may have the syndrome, who then require confirmation with further genetic (germline) testing.

LS results from an inherited germline mutation in a group of DNA damage response genes responsible for biologic mechanisms of mismatch repair (MMR), specifically MLH1, MSH2, MSH6, PMS2, or EPCAM.[28] Alterations affecting the normal function of these genes results in an accumulation of DNA errors and increases the potential for cancer development. Tumor tissue testing by histologic studies such as IHC can indicate loss of these specific MMR proteins or evaluate for MSI status as a

standard means to assess for the possibility of LS-association. Suspicious findings with these tests require further confirmatory testing, for which patients should be referred to a specialist for genetic counseling.

Recommendations and guidelines in other LS-related cancers strongly endorse universal MMR and MSI testing. A detailed analysis by the Evaluation of Genomic Applications in Practice and Prevention (EGAPP) Working Group from the CDC reported sufficiently strong evidence to recommend genetic testing routinely be offered to all patients with newly diagnosed colorectal cancers (CRC) due to the high rate (3%) of LS and the indication of significant, cost-effective clinical benefits for patients and family members.[28] Of the strategies investigated and endorsed, reflex IHC studies for MMR and MSI testing were highlighted for their high sensitivity and specificity. The Panel acknowledges the EGAPP report did not evaluate or address testing in UTUC but similarly endorses an analogous strategy in that the Panel recommends genetic testing to all patients with UTUC due to the higher identified prevalence of LS association in UTUC relative to CRC.

Table 4: Clinical Screening Criteria for LS (also referred to as hereditary non-polyposis colorectal cancer [HNPCC])

Amsterdam II	**Three relatives with any LS-associated cancer (colorectal cancer, cancer of the endometrium, small bowel, UTUC)**
	Two successive generations should be affected
	One should be a first-degree relative of the other two
	One should be diagnosed before age 50
Revised Bethesda Guidelines	Tumors in families that meet Amsterdam II criteria
	Colorectal cancer diagnosed in a patient who is less than 50 years of age
	Presence of synchronous, metachronous colorectal, or other LS-associated tumors, regardless of age
	Colorectal cancer with MSI-high testing diagnosed in a patient who is less than 60 years of age
	Colorectal cancer diagnosed in one or more first-degree relatives with an LS-related tumor, with one of the cancers being diagnosed under age 50 years
	Colorectal cancer diagnosed in two or more first- or second-degree relatives with LS-related tumors, regardless of age

Adapted from *Revised Bethesda Guidelines for Hereditary Nonpolyposis Colorectal Cancer (Lynch Syndrome) and Microsatellite Instability* and *New clinical criteria for hereditary nonpolyposis colorectal cancer (HNPCC, Lynch syndrome) proposed by the International Collaborative group on HNPCC*.[29, 30]

The NCCN Guideline *Genetic/Familial High-Risk Assessment: Colorectal version 1.2022* endorses universal MMR testing of all CRC and endometrial cancers and recommends considering universal testing of other LS-related malignancies regardless of the age of diagnosis including urothelial cancers. These recommendations are founded on findings from a large data set of over 15,000 LS-related cancers (including 551 urothelial cancers) screened with MSI, MMR and germline genomic testing which identified LS-association in over 16% of cases of patients with MSI-high signatures and specifically 37.5% in urothelial cancer cases.[27]

From the guideline systematic review, four retrospective cohort studies were identified that evaluated factors associated with LS in patients diagnosed with UTUC.[31] Although the patient numbers in these series were modest, limiting the analyses, the use of MMR and MSI testing was significantly associated with identification of LS patients within studied cohorts when used adjunctively with standard clinical screening criteria. One study evaluated a universal molecular screening strategy against a genetic testing standard. Patients who screened positive by standard clinical criteria (Amsterdam II), had loss of one or more MMR proteins, or had high MSI, were considered to have "potential LS," and were referred for germline testing. Of 115 patients screened, 13.9% had potential LS: 7.0% met Amsterdam II criteria; 11.3% had loss of at least one MMR protein; and 5.7% had high MSI. Of the 16 patients with potential LS, 9 completed germline testing, with LS confirmed in 6 patients (5.2% of the total 115 patients screened). These data are comparable with described results from large cohort screening studies in LS malignancies.[27]

It must be acknowledged that MMR or MSI studies are screening tests and are neither genetic tests nor a gold standard for identifying LS. As such, these tests may miss 10% or more with the disease.[32] Germline genetic testing, also considered a molecular study, is a more definitive means of diagnosis requiring specific counseling and justified if available – yet may also fail to identify familial cases of Lynch-like syndromes caused by epigenetic phenomena. Universal molecular testing serves a key role along with clinical awareness when evaluating UTUC patients providing the opportunity for discussion of genetic risk factors with patients and sufficient indication for appropriate genetic counseling referral for any patient with UTUC. The Panel notes that identifying the presence of LS-associated and MSI-high cancers also has clinical implications related to therapeutic treatment options, including identified sensitivity of urothelial cancers with mutations in DNA damage repair genes to systemic agents such as immune checkpoint inhibitors and cis-platinum-based chemotherapy.[33, 34]

RISK STRATIFICATION

9. **At the time of identified UTUC, clinicians should perform a standardized assessment documenting clinically meaningful endoscopic (focality, location, appearance, size) and radiographic (invasion, obstruction, and lymphadenopathy) features to facilitate clinical staging and risk assessment. (*Strong Recommendation; Evidence Level: Grade B*)**

Tumor features identifiable by endoscopic and radiologic assessment are strongly associated with disease risk and, therefore, necessary to properly inform risk stratification, treatment decision-making and assessment of treatment response.[35-41] Standard reporting of endoscopic findings is, therefore, critical to document and communicate objective clinical findings. At the time of examination by antegrade or retrograde approach, clinicians should document key features including the following:

- Sites of involvement (ureteral segment, renal pelvis, calyceal sites and lower tract)
- Number of tumors or presence of multifocality
- Tumor appearance (sessile, papillary, flat/villous)

It is also recommended that documentation include an estimate of the largest tumor size, if possible, by using a reference standard such as the scope tip, basket, laser fiber, biopsy forceps, or brush. Quality of visualization can impact the accuracy of endoscopic inspection (e.g., bleeding, difficulty in access, tumor location, artifacts from instrumentation) and should be documented in endoscopic reports.

Radiographic characterization of tumor features is also informative for clinical staging. As noted, retrograde urography should be performed concomitantly with upper tract endoscopic assessment and documentation of filling defects or evidence of urinary tract obstruction should be provided. Reporting from contrast-enhanced cross-sectional imaging should include details of tumor characteristics that suggest invasive features, obstruction of the urinary tract, and locoregional progression such as suspicious lymphadenopathy, and/or presence of metastatic disease.

10. **Following standardized assessment, clinicians should risk-stratify patients as "low-" or "high" risk for invasive disease (pT2 or greater) based on obtained endoscopic, cytologic, pathologic, and radiographic findings. Further stratification into favorable**

and unfavorable risk groups should then be based on standard identified features (Table 5). (*Strong Recommendation; Evidence Level: Grade B*)

Determining cancer-associated risk is critical to guide risk-adapted treatment selection and patient counseling. Tumor characteristics determined from the standardized process of clinical assessment described in this guideline allows categorization of tumors into high- and LR groups. The association of HG cancer (HG biopsy or cytology) with disease progression risk and pathologic stage T2 or greater disease defines the category of HR whereas LG cancer (LG biopsy and normal cytology) defines LR disease.

It is recognized that heterogeneity within these two categories exists, warranting further stratification by distinct clinically identifiable features. The factors below highlight these additional findings to aid sub-stratification within the HR and LR categories and to guide risk-adapted management strategies. An accounting of the data supporting these additional features is also included in Appendix tables II and III.

BIOPSY

The association of HG tumor on ureteroscopic biopsy with high-stage (HS) disease (≥pT2) on final pathology (13 studies, N=1,197) has a PPV of 60% (95% CI: 54% to 66%; range: 33% to 85%; I^2 = 57.0%) and a pooled NPV of 77% (95% CI: 73% to 82%; range: 67% to 100%; I^2 = 19.8%), indicating room for further refinement along the spectrum of favorable to unfavorable within the HR and LR groups.[42] Sub-stratification features have been identified and reported in publications and nomogram formats and are recognized by the guideline Panel as being useful for further risk refinement.

CYTOLOGY

Selective ipsilateral upper tract cytology provides supplemental histologic data to tumor biopsies and the finding of HG cytology in the setting of LG biopsy findings indicates the likely presence of higher-risk features (e.g., HG tumor) missed on biopsy sampling. Obtaining selective cytology after tumor biopsy can improve the yield of cells for cytologic analysis.[43]

FISH

There are limited data on the independent value of FISH testing to identify advanced stage disease, and its routine use for this purpose cannot be supported now. The association of FISH with the presence of a HG tumor is recognized and may have value as an adjunct test in some scenarios where tissue sampling is challenging and cytology is indeterminate. Two studies (N=244) reported on the diagnostic accuracy of FISH for identifying HS disease in confirmed UTUC.[44, 45] The studies used the reference standard of histologic confirmation on final surgical pathology report from NU or distal ureterectomy and defined HS as ≥pT2. Sensitivity was from 72% to 83% and specificity was 38% to 47%, for PPV of 58% to 60% and NPV of 63% to 67%. One of the studies found that FISH results were not significantly associated with increased likelihood of HS disease (p=0.12).[45]

IMAGING

CT

The sensitivity and specificity of specific CT findings for identifying *HG disease* varies (Appendix II); the CT finding with the best combination of sensitivity and specificity was presence of heterogeneous texture (versus homogeneous; sensitivity: 70% and specificity: 100%) with a PPV of 100% and a NPV of 28%.[46, 47] However, these predictive values should be interpreted with caution due to a low proportion of patients with LG UTUC in the study cohort. The presence of ipsilateral hydroureteronephrosis demonstrates limited diagnostic accuracy for the findings of HG UTUC, with a sensitivity of 40% to 43% and specificity of 60% to 66%, which was further supported by a study by Ng et al. in which hydronephrosis on CT was not significantly associated with HG UTUC (p=0.49).[47]

Similarly, the sensitivity and specificity of specific CT findings for identifying *HS* UTUC, which is defined as ≥pT2, is variable. Five studies reported on the diagnostic accuracy of CT for identifying HS disease in confirmed UTUC.[46-50] Heterogenous texture on enhanced and even unenhanced CT imaging has been associated with invasive disease.[51] In a study of 48 patients with UTUC, the presence of heterogeneous (versus homogenous) texture was associated with the best combination of sensitivity (91%) and specificity (58%) for advanced stage, with a PPV of 66% and NPV of 88%. In this series, identification of hydronephrosis on CT was associated with a 4-fold increase in the risk of HS UTUC (hazard

ration [HR]: 4.0; 95% CI: 1.4 to 11.5, p=0.01). The sensitivity of multidetector CT identifying HS disease (≥pT3) ranges from 0.28 – 0.75, while the specificity ranges from 0.84-1.00.[46, 48, 50] Specific features that have been proposed to predict HS UTUC include the presence of local invasion on CT and the presence of pathologically enlarged lymph nodes, both of which are associated with a relatively modest sensitivity of 0.49 and 0.22, respectively, with a higher specificity (0.85, and 0.98, respectively).[49]

OTHER IMAGING

Retrograde pyelograms provide a roadmap for evaluation and possibly planning kidney-preserving strategies and should be considered at initial evaluation with images retained in the patient record. Modalities such as endoluminal US do not yet have a well-defined clinical role and warrant either prospective evaluation or, at a minimum, further testing under controlled clinical circumstances such as quality improvement studies. MRI can provide some soft tissue details in patients who cannot receive contrast, offering some advantages in such patients by identifying features of fat invasion with diffusion weighted imaging associated with very advanced, T3 disease.[52] However, MRI can falsely over-estimate tumor stage due to surrounding tissue effects that may mimic tumor invasion such that establishing cutoffs for diffusion weighted imaging have not been well established.[53] At present, the Panel recommends such studies only as supplements to current standards of care.

Table 5: Presurgical Clinical Risk Categories

Risk Stratification				
Feature	***Low-risk***		***High-risk***	
Biopsy Grade	Low-Grade		High-Grade	
Sub-stratification	*Favorable*	*Unfavorable*	*Favorable*	*Unfavorable*
Cytology*	Negative cytology	No HGUC	Any Cytology	HGUC
Radiography	No invasion	No invasion	No Invasion	Invasion
	No obstruction	Obstruction	No obstruction	Obstruction
	Normal nodes	Normal nodes	Normal nodes	Suspicious nodes
Appearance	Unifocal	Multifocal	Unifocal	Multifocal
	Papillary	Papillary	Papillary	Sessile or Flat
Lower Tract Involvement*	No involvement	Involvement	No involvement	Involvement
Therapy				
Ablative Treatments	Preferred	May be offered	Rare, selected cases	Palliation
Systemic Therapy	Not recommended	Not recommended	Neoadjuvant or adjuvant	Neoadjuvant or adjuvant

* Per the Paris system criteria for interpretation of urinary cytology which recognizes 7 categories for cytology reporting: nondiagnostic, negative for HG urothelial carcinoma (NHGUC), atypical urothelial cells (AUC), suspicious for HG urothelial carcinoma (SHGUC), HG urothelial carcinoma (HGUC), LG urothelial neoplasm (LGUN), and other malignancies.

** Concomitant or prior history of lower tract involvement.

TUMOR APPEARANCE, GROWTH CHARACTERISTICS AND LOWER TRACT INVOLVEMENT

Tumor features associated with more aggressive cancer risk include sessile versus papillary appearance, multi-focality, and, relatedly, pan-urothelial disease as indicated by history of prior cystectomy, concomitant or metachronous lower tract urothelial cancer or contralateral UTUC diagnosis.[54, 55] Each of these features are considered unfavorable if present. Recognizing no single finding can reliably provide adequate staging or risk-stratification in isolation, several groups have tried to combine multiple variables to strengthen predictive ability. The Panel acknowledges the debate on issues including overlap in several of these features and aspects of additive risk when more than one feature is present, describing a spectrum of risk, which can be weighted and considered during shared decision-making and treatment election.

OTHER FEATURES

The Panel recognizes that other features have been identified that may have an association with disease risk (e.g.., tumor size, lymphovascular invasion (LVI) neutrophil-to-lymphocyte ratio, tp53 or FGFR3 mutation status). However, these variables may not be widely available, easily identified or measured, thereby limiting broad applicability. Specifically, tumor size has a described association with tumor grade and stage; however, measurement in the pre-surgical setting is not standardized and has not been shown to be independent of other more easily determined clinically identified features such as multifocality, invasion and obstruction. Importantly, data supporting tumor measurements from large retrospective databases have been derived from pathology reports after surgical resection and may not be applicable to pre-operative imaging or endoscopic tumor size estimates – therefore less clinically useful.[56]

11. **Patients with UTUC should be assessed prior to surgery for the risk of post-NU CKD or dialysis. (*Expert Opinion*)**

Initial decisions regarding operative approach and administration of systemic therapy are based on patients' baseline renal function and their estimated post-operative estimated glomerular filtration rate (eGFR). Patients undergoing NU have diminished postoperative renal function due to loss of a renal unit. A median decline in renal function after NU up to 32% has been reported which can induce or exacerbate a state of CKD, affect a patient's candidacy to receive adjuvant chemotherapy.[57, 58]

Patients with UTUC should, therefore, undergo an assessment of renal function and, for individuals who are scheduled to undergo NU and especially those who may require perioperative systemic treatment, an estimation of post-operative renal function should be made. Recommended tests include serum creatinine to calculate an eGFR and, at the clinician's discretion for more refined evaluation, split function testing such as with differential renal scan or CT volumetric studies. Perioperative nephrology consultation can be considered as well, particularly in patients with pre-existing kidney disease. Attention should be paid in the settings of renal atrophy and hydronephrosis, which may alter clinical estimates of resulting post-operative renal function. Hydronephrosis caused by tumor obstruction may falsely *under-estimate preoperative* renal function and alter decision-making around the use of neoadjuvant chemotherapy (NAC). Thus, in settings of hydronephrosis, renal decompression either by indwelling ureteric stent or a percutaneous nephrostomy tube placed in an uninvolved renal calyx along with oral fluid hydration for 7-14 days before re-checking eGFR will help to establish a more accurate estimation of baseline renal function. Ureteric stenting is the preferred method of drainage given the known risk of tract seeding with percutaneous nephrostomy tubes in the setting of UTUC as well as quality of life considerations[59] Atrophy of the contralateral (unaffected) renal unit may lead to *over-estimates of postoperative* renal function in the setting of NU since the kidney with lower differential function will remain *in situ*[60, 61] Results of renal function investigations can help with patient counseling, strategizing treatment sequence, and determination of downstream risks of CKD and potential dialysis. In patients with sufficiently poor CKD in which NU could precipitate ESRD, a post operative plan for dialysis in conjunction with nephrology colleagues should be in place preoperatively including plans for dialysis access. Referral to nephrology for detailed evaluation and recommendations for perioperative management is warranted in such cases.

In patients with pre-existing CKD or a solitary kidney, attempts to preserve renal function can be made, if

oncologically feasible and appropriate, with segmental or endoscopic organ-sparing approaches which preferentially are associated with improved postoperative renal function.[62-64] Notably, in four studies reporting the impact of SU compared to NU on renal function, three found SU was associated with improved renal function versus NU with differences in eGFR ranging from 14 to 19 mL/m.[65-67]

As stated in the Renal Mass and Localized Renal Cancer: Evaluation, Management, and Follow Up: AUA Guideline,[68, 69] predictive factors for post-operative development of CKD or progression of pre-existing CKD include older age, diabetes mellitus, hypertension, as well as male sex, obesity, tobacco use, larger tumor size, and post-operative acute kidney injury.[70-76] Patients who present with eGFR less than 45 mL/ min/1.73m^2 or confirmed proteinuria are at particularly HR from a functional standpoint and should be considered for nephrology consultation. Patients who are expected to have an eGFR less than 30 mL/ min/1.73m^2 after intervention will also be at HR long-term, and a nephrologist should be involved in their care. Identifying modifiable risk factors including diabetes mellitus (DM), hypertension (HTN) and smoking is essential. Optimizing glycemic and blood pressure control, smoking cessation and minimizing risk of acute kidney injury (with avoidance of hypotension and nephrotoxic agents such as intravenous contrast or non-steroidal anti-inflammatory drugs) should reduce the degree of renal dysfunction in the perioperative period.[77] Of note, patients with DM are at even higher risk for acute kidney injury compared with those without DM, even among those with normal eGFR prior to nephrectomy.[70] With significant nephron mass loss, hyperfiltration can occur resulting in glomerular damage, exacerbation of proteinuria and progressive sclerosis with further decline in GFR. Therefore, repeat assessment of blood pressure, eGFR, and proteinuria should be performed soon after nephrectomy then again in three to six months to assess for development or progression of CKD. With any compromise in eGFR or presence of CKD complications, additional regular monitoring of kidney function should be performed and further management of CKD would be recommended with referral to nephrology. Careful management of DM and HTN and avoidance of substantial weight gain may slow or prevent CKD progression and should be prioritized on a long-term basis.

TREATMENT

12. **Clinicians should provide patients with a description of the short- and long-term risks associated with recommended diagnostic and therapeutic options. This includes the need for endoscopic follow-up, clinically significant strictures, toxicities associated with surgical treatment and side effects from neoadjuvant and adjuvant therapies. (*Clinical Principle*)**

Providing patients with a detailed description of risks and benefits associated with treatment options is a mandatory requirement of care, and clinicians must be familiar with outcomes in upper tract management. Urothelial recurrences are common in the management of UTUC, regardless of approach, and mandate long-term surveillance for which patients must be prepared – including the potential need for additional treatments. Ablative options can provide local control including durable long-term kidney sparing outcomes but incur additional endoscopic surveillance requirements and associated risks such as stricture and infection.[78] Specifically, the use of chemoablative treatment with the reverse thermo-hydrogel preparation of mitomycin for pyelocaliceal instillation for LG tumors carries an FDA label warning for ureteral obstruction (>44%), bone marrow suppression, and embryo-fetal toxicity.[79] Systemic chemotherapy and immunotherapy treatments also have toxicities requiring specific counseling best provided as part of multi-disciplinary care.

Kidney Sparing Management

13. **Tumor ablation should be the initial management option for patients with LR favorable UTUC. (*Strong Recommendation; Evidence Level: Grade B*)**

LR UTUC is associated with low rates of metastatic progression and presents an opportunity for kidney preservation. Endoscopic management (by retrograde ureteroscopy, antegrade ureteroscopy, or percutaneous resection) is an established treatment option for urothelial cancer, including those involving the upper tract, and should be the first-line treatment for patients with LR favorable UTUC when technically feasible. Developing RCTs is a challenge in this setting since renal functional loss from NU represents a significant medical risk, leaving

a small number of patients at individual centers with normal renal function who might be considered trial-eligible. There are 13 observational studies that have compared endoscopic management with NU showing similar cancer-specific survival (CSS) and improved renal functional outcomes for patients treated with endoscopic ablation.[62-64, 80-89] As these are retrospective studies, characteristics of patients selected for endoscopic management versus those managed with NU are varied and results must be interpreted in the context of strong case-selection bias. A study by Grasso et al. (n=162) with a mean follow-up just over 3 years reported improved 5-year CSS for patients with LG UTUC who underwent ureteroscopic management versus those with any grade UTUC who underwent NU in which 10-year DSS were similar (5-year: 87% versus 64%; 10-year: 81% versus 78%).[82] Further, studies by Rouprêt et al. (n=97) and Shenhar et al. (n=61) reported similar 5-year CSS for patients who underwent endoscopic management and NU (80% to 81% versus 84% and 89% versus 92%, p=0.96).[64, 85]

Regarding renal functional outcomes, two studies [81, 87] reported similar renal function following endoscopic management or NU, and three studies reported better renal outcomes following endoscopic management.[62-64] Four studies reported similar rates of surgical complications or reported no statistically significant differences.[64, 81, 84, 85]

In certain clinical scenarios of LR UTUC, complete endoscopic ablation may not be feasible. Such instances may be predicated on specific tumor (location and focality) and patient factors (age, comorbidities, baseline renal function, procedural risk). Chemoablation (in-situ tissue destruction) can be a treatment alternative in these situations. In an open label, single arm, phase III trial in patients with LG tumors measuring between 5 – 15 mm, Kleinmann et al. reported that a mitomycin containing reverse thermal gel yielded a 59% (42 of 71 renal units) complete response at primary disease evaluation, 1 month following a 6-week course of therapy.[79] A subsequent report from these investigators highlighted that 56% of evaluable complete responders remained disease free at 12 months post-therapy.[78] The observed benefit of mitomycin containing reverse thermal gel in these studies must be balanced against the risk of possible ureteral stricture. Importantly, chemoablation should not be used as a substitute for complete endoscopic ablation whenever feasible.

14. Tumor ablation may be the initial management option offered to patients with LR unfavorable UTUC and select patients with HR favorable disease who have low-volume tumors or cannot undergo RNU. (*Conditional Recommendation; Evidence Level: Grade C*)

There is no high-quality evidence that specifically compares outcomes of endoscopic management versus NU for patients who meet specific criteria for LR unfavorable or HR favorable UTUC. Collectively, comparable cancer-specific survival and improved renal functional outcomes are reported for patients undergoing endoscopic management relative to NU (see discussion in the Guideline statement 13).[62-64, 80-89] Some studies have included in their analyses patients with features of unfavorable LR disease (e.g., multifocal LG tumors).[81, 82, 90] Further, Grasso et al. included patients with pan-urothelial disease and larger tumors but did note a higher rate of disease progression in these patients.[82]

Tumors < 1.5 cm in size may be optimal for endoscopic ablation given a lower risk of invasive disease. Conversely, tumors ≥ 1.5 cm in size are associated with a > 80% risk of invasive disease, and tumors > 2.5 cm are associated with a lower disease-specific survival.[91] Further, hazard ratio analyses of tumor size cutoffs of 1.5 and 2 cm have demonstrated significant relationships with stage ≥ pT2.[92]

Endoscopic ablation has been reported in patients with imperative indications with tumors up to 6.0 cm. Scotland et al. described their institutional experience treating patients with tumors ≥ 2.0 cm in size and found 5-year recurrence-free survival (RFS), progression-free survival (PFS), and CSS rates of 10%, 65%, and 84%.[93] Therefore, larger tumors (≥ 1.5 cm) may be considered for ablation based on the provider's experience and assessment of the need for kidney sparing surgery.

For patients with LR unfavorable disease who demonstrate progression in tumor size, focality, or grade, the Panel recommends against further endoscopic-assisted attempts and consideration of definitive resection via segmental ureterectomy (SU) or NU. In cases of HR favorable cancers managed endoscopically, clinicians must recognize the higher risks of disease

progression and pivot early to definitive surgical resection when necessary.

15. **Tumor ablation may be accomplished via a retrograde or antegrade percutaneous approach and repeat endoscopic evaluation should be performed within three months. (*Expert Opinion*)**

Various approaches and techniques may be employed to successfully treat UTUC by ablation. Retrograde approaches including ureteroscopy with pyeloscopy is commonplace, while percutaneous techniques including antegrade pyeloscopy or ureteroscopy with ablation is typically reserved for larger tumors, those that are difficult to access in a retrograde fashion, or in patients who have undergone prior radical cystectomy or urinary diversion.

The energy source employed for ablation may vary based on availability of instrumentation and tumor characteristics. Thulium laser, holmium laser, Neodymium (Nd:YAG), and electrocautery devices (e.g., Bugbee) may all be deployed through an endoscope. Additionally, chemoablation may be employed either through retrograde ureteral catheter instillation or percutaneous access with fluoroscopic imaging guidance.

Optional use of a ureteral access sheath during the time of ureteroscopic ablation can provide some advantages for endoscopic assisted ablation when safely employed – allowing for repeated scope passage up and down the ureter for sampling and a means of fluid egress from the upper tract to avoid excess pelvicalyceal hydrostatic pressure from irrigation solutions. A study by Douglawi et al. demonstrated a lower rate of intravesical recurrence in patients who underwent ureteroscopy with an access sheath compared to those without a sheath prior to NU.[94] Prior to placement of any ureteral access sheath, the entire ureter should be directly visualized in order to avoid missing any luminal neoplasms, especially in the distal ureter.

Repeat endoscopic evaluation should take place within three months of the initial treatment due to the proclivity of UTUC to recur and for residual disease to remain after the first ablation. Optimal timing of follow-up endoscopic evaluation has not been well established noting that several factors may impact the indication and decision for short interval follow-up such as aspects of visualization. A study of 41 patients who underwent a second look ureteroscopy within 60 days of ablation showed a 51.2% cancer detection rate at the time of the second look.[95] A 30-day window on either side of this endpoint (i.e., 30 to 90 days) is justified to allow timely identification of recurrences and may be dictated by aspects such as tumor size, visualization, access, treatment efficacy, etc., as clinically indicated. Clinicians may wish to take a conservative approach with shorter interval endoscopic diagnostic and therapeutic endoscopic procedures for more challenging cases, particularly when incomplete treatment is a possibility. Repeat endoscopic assessment should occur within three-month intervals until no evidence of upper tract disease is identified.

16. **Following ablation of UTUC tumors and after confirming there is no perforation of the bladder or upper tract, clinicians may instill adjuvant pelvicalyceal chemotherapy (*Conditional Recommendation; Evidence Level: Grade C*) or intravesical chemotherapy (*Expert Opinion*) to decrease the risk of urothelial cancer recurrence.**

There is ample evidence supporting the use of an immediate instillation of intravesical chemotherapy at the time of transurethral resection of a bladder tumor for urothelial carcinoma for the purpose of reducing the rate of intravesical tumor recurrence.[96, 97] The principle of an immediate instillation of intravesical or pyelocaliceal (upper tract) chemotherapy at the time of endoscopic tumor ablation for UTUC is undertaken by extrapolation of the data supporting this practice in the management of urothelial carcinoma of the lower tract. At present, this is considered an optional part of routine practice. The available reported clinical experience reported in the upper tract is less compelling. A small, prospective, non-randomized single center cohort study by Gallioli et al., showed a strong trend in improving urothelial recurrence free survival (URFS) for patients treated with a single upper tract instillation of Mitomycin C after endoscopic ablation. Mean URFS was 29 months for the treated group compared to 19 months in patients who did not receive treatment (log-rank p = 0.067).[98] Though a small study including only 51 patients, there were controls for several potential confounding variables and low ROB was identified. A larger study (n=73) by Cutress et al. did not control for confounding variables and failed to identify a difference in RFS with adjuvant intraluminal chemotherapy.[99] In the Gallioli study, the majority of recurrences were observed in the bladder.[98] More recent work has explored the role of an adjuvant dose of upper

tract mitomycin gel following endoscopic ablation with a report of 63% ipsilateral disease-free rate at 6.8 months following instillation, albeit with a 19% ureteral stenosis rate and no comparator group.[100] While acceptable, there are limited direct supporting data for this common practice in upper tract applications at this time.

Technical Considerations

The optimal administration technique is not fully elucidated. Both *ex vivo* and *in vivo* porcine models suggest higher rates of topical therapy delivery to the pyelocaliceal system with retrograde administration by ureteral catheter.[101-104] However, the Panel considers each of the following delivery approaches to be acceptable: 1) antegrade perfusion by nephrostomy tube, 2) retrograde perfusion via ureteral catheter, and 3) bladder instillation by transurethral catheter with reflux via a double J ureteral stent. In the third scenario, it is recommended to perform a cystogram and demonstrate adequate reflux of contrast into the pyelocaliceal system. Finally, while bacillus Calmette-Guerin (BCG) is the mainstay of topical therapies for UTUC, the following agents have been described: mitomycin c, gemcitabine, docetaxel, epirubicin, adriamycin, thiotepa, and BCG with interfero[105, 106]

17. Pelvicalyceal therapy with BCG may be offered to patients with HR favorable UTUC after complete tumor ablation or patients with upper tract carcinoma in situ (CIS). (*Expert Opinion*)

Topical therapy may consist of a six-week induction course of BCG. Patients should be considered for topical therapy if imperative indications are present, including solitary kidney status, bilateral UTUC, or risk of progression to end-stage renal disease.

There is a dearth of literature specifically regarding the treatment of favorable HR UTUC with topical therapy (e.g., BCG). No randomized trials exist to compare outcomes of patients treated with topical therapy versus NU, and retrospective comparisons are limited by small cohorts.[101] However, several small observational studies have evaluated the role of BCG as the primary treatment of upper tract CIS (UTCIS) and as an adjuvant treatment for Ta/T1 disease. These studies have been summarized in systematic reviews.[102, 105] Regarding the treatment of CIS, generalizations of the literature are limited by the lack of a standard definition of UTCIS, variable methods of UTCIS detection (voided cytology, selective, cytology, ureteroscopic visualization, biopsy), and inconsistent measurements of successful treatment. These systematic reviews report rates of complete response ranging from 41% to 100%. Rates of recurrence, progression, and transition to radical NU likewise vary from 10% to 46%, 0% to 45%, and 45% to 100%, respectively. Further, AEs are reported in 0% to 92% of patients across studies and include cystitis, fever, sepsis, renal tuberculosis, ureteral stricture, and pericarditis.[102, 105]

Regarding the treatment of UTUC Ta/T1 disease, Foerster et al. conducted a meta-analysis of 12 non-randomized observational studies including 212 patients who underwent adjuvant therapy following ablation of Ta/T1 disease.[106] Median follow-up was 31 months, during which time 39% of patients developed a recurrence. Nine studies (with ≥ 10 patients) were included for pooled survival estimates. CSS and overall survival (OS) were 94% (95% CI: 86 to 99%), and 71% (95% CI: 47 to 90%), respectively. One study included in the analysis included 22 renal units with Ta/T1 disease and reported progression in 41% of patients.[107] Although most studies have used BCG as the therapeutic agent, sub analyses showed no significant differences in outcomes when other agents were administered.

18. When tumor ablation is not feasible or evidence of risk group progression is identified in patients with LR UTUC, surgical resection of all involved sites either by RNU or segmental resection of the ureter should be offered. (*Moderate Recommendation; Evidence Level: Grade C*)

Failure of conservative strategies for kidney preservation includes the risk of cancer progression, potentially shifting from curable to an incurable form of UTUC. Clinical evidence of a change in tumor growth pattern toward a more aggressive subtype should prompt re-assessment of management strategy and consideration for more definitive treatment with extirpative surgical resection. This is especially true for LG cancers, which should not display evidence of aggressive biology including invasion, multifocal implantation, HG cytology, or change from non-obstructing to obstructing tumors. Such features should prompt a detailed discussion with patients about the observed findings, their clinical significance suggesting a shift in disease risk and consideration for change in strategy developed through shared decision-making.

Data on outcomes comparing endoscopic management to extirpative surgery in different risk groups are limited but provide support for this transparent approach to counseling and managing patient expectations.

Thirteen retrospective studies compared endoscopic management versus RNU with baseline differences between treatment cohorts noted.[62-64, 80-89] Eight studies compared RFS.[62-64, 80, 81, 83-86, 89] Of three groups that reported adjusted risk estimates, one (n=120) found endoscopic management was associated with an increased risk of any (local, intravesical, or distant) recurrence (adjusted HR: 3.56; 95% CI: 1.73 to 7.35),[84] one study found endoscopic management associated with improved intravesical RFS (adjusted HR: 0.56; 95% CI: 0.25 to 1.25),[81] and one found endoscopic management associated with increased risk of local recurrence (adjusted HR: 1.27; p=0.001) but no difference in risk of intravesical RFS (adjusted HR: 0.90; p=0.52).[86] Nine studies reported outcomes on CSS or all-cause mortality (ACM).[62, 80-87] Three (n=453, 356, and 170) that controlled for confounding factors found endoscopic management was associated with worse CSS (propensity-matched HR: 2.1; 95% CI: 1.0 to 4.1; adjusted HR: 1.18; p=0.12; adjusted HR: 2.00; 95% CI: 0.33 to 12.50).[81, 86, 89] Valid concerns for aspects such as accuracy of clinical staging, risks of undiagnosed HG cancers and disease-specific mortality associated with developing HR disease warrants vigilance in follow-up and recognizing clinical signs indicating thresholds for recommending altering care.

19. Clinicians may offer watchful waiting or surveillance alone to select patients with UTUC with significant comorbidities, competing risks of mortality, or at significant risk of End-Stage Renal Disease (ESRD) with any intervention resulting in dialysis. (*Expert Opinion*)

Some patients with UTUC have significant comorbid medical conditions that impose serious risks of severe, treatment-related complications from any form of intervention. Complication rates following RNU range from 15% to 50% including a 30-day mortality risk of 1%.[108] Such results do not reflect outcomes in non-operative cases where observation and palliative approaches are utilized. Discussion of treatment related risks including perioperative mortality may lead to a shared decision to proceed with active surveillance (whereby periodic assessments such as imaging or limited endoscopic assessment are performed) or watchful waiting/expectant management, where interventions are limited to palliation or awaiting symptomatic progression – especially in those with very limited life expectancy. In such cases, patients and family should be counseled and prepared for disease-related events such as bleeding, obstruction, infection, and pain with options for palliation that may be limited.

Two studies utilizing large databases compared non-surgical management versus surgery for UTUC.[109, 110] Both studies found non-surgical management was associated with worse OS versus surgical treatment though likely reflecting the compromised medical condition of these patients. Outcomes reported from the SEER database (n=8,304; 633 of whom did not undergo surgery) also observed that non-surgical management was associated with worse OS (median 1.9 versus 7.8 years; p<0.001) and 3-year CSS (74% versus 92%; p<0.001).[110] Another study utilized the National Cancer Database (n=28,910; 3,157 of whom did not undergo surgery) and similarly found non-surgical management to be associated with worse OS (median 2.0 versus 5.6 years; p<0.0001).[109]

Surgical Management

20. Clinicians should recommend RNU or SU for surgically eligible patients with HR UTUC. (*Strong Recommendation; Evidence Level: Grade B*)

RNU with complete bladder cuff excision (BCE) and lymphadenectomy is the standard of care for patients with HR UTUC. Principles of RNU include complete excision of ipsilateral upper tract urothelium, including the intramural portion of the ureter and ureteral orifice with negative margins, and avoidance of urinary spillage, such as by early low ligation of the ureter, to minimize the risk of seeding urothelial cancer outside the urinary tract.

The RNU specimen should be removed *en bloc* whenever technically feasible. Open, robotic, and laparoscopic approaches are suitable for RNU so long as the above oncologic and surgical principles are adhered to. The systematic literature review supporting these guidelines demonstrated equivalent oncologic outcomes for open and minimally invasive (laparoscopic, hand-assisted laparoscopic, robot-assisted laparoscopic) approaches to RNU.[111] Minimally invasive approaches were associated

with favorable perioperative outcomes including shorter length of stay and fewer complications, and, therefore, are favored for most patients when principles of RNU can be maintained. Case selection criteria are difficult to assess in these analyses such that outcomes across the range of tumor staging could be a concern and used as rationale for preferentially offering open surgical approaches for large, bulky UTUC with clinical evidence for direct invasion to adjacent structures.[112]

Numerous studies demonstrate worse local and metastatic recurrence rates with associated decreased CSS and OS for patients who did not receive complete BCE.[111] BCE can be completed either extravesically or transvesically through a variety of approaches including open, minimally invasive or transurethral endoscopic techniques. Transurethral endoscopic approaches are associated with higher recurrence rates in the bladder and may limit the ability to utilize post-NU intravesical therapies if the bladder is not fully closed.[113]

Ureterectomy including SU with ureteroureterostomy and distal ureterectomy with ureteral reimplant are reasonable alternatives to RNU for well-selected patients. The literature review demonstrates equivalent oncologic outcomes for patients undergoing RNU and ureterectomy recognizing the inherent selection differences in the comparative cohorts.[111] The most favorable candidates for distal ureterectomy are patients who have ureteral tumors in the lower third of the ureter and a sufficiently mobile bladder with capacity to facilitate reimplantation with or without reconfiguration of the bladder to facilitate a tension-free anastomosis (i.e., Boari flap or psoas hitch maneuver). Patients most suitable for SU have small, unifocal tumors (typically 1 cm or smaller) tumors isolated to a short segment of the proximal or mid-ureter requiring resection of 2 cm or less of ureteral length to allow for primary ureteroureterostomy. Longer sections of ureteral involvement and resection may require more complex reconstruction techniques when kidney sparing is desired. Principles of ureterectomy in select cases include:

- Patient counseling to describe techniques, potential requirements for urinary reconstruction and associated complications including the potential impact on postoperative bladder function.
- Preoperative endoscopic assessment to evaluate sites of involvement and proximal extent of disease.
- Preoperative assessment of bladder capacity and function in cases where more extensive reconstruction such as a Boari flap are anticipated to permit a tension free ureterovesical anastomosis or the use of bowel segments.
- Intraoperative pathologic assessment (i.e., frozen sections) of proximal and distal margins to ensure complete resection with negative margins.
- Reasonable attempts to avoid of spillage of urine into the surgical field.
- Watertight, tension free closure to facilitate functional healing and avoid urine leak (of urine potentially contaminated with malignant cells).

21. For surgically eligible patients with HR and unfavorable LR cancers endoscopically confirmed as confined to the lower ureter in a functional renal unit, distal ureterectomy and ureteral reimplantation is the preferred treatment. (*Expert Opinion*)

Distal ureterectomy and reimplantation offers definitive curative management for tumors confined to the lower ureter while preserving kidney function. It is, therefore, the treatment of choice for patients with localized cancers in this location with an increased risk of disease recurrence and progression. Other approaches such as endoscopic assisted tumor ablation are considered alternative options to the gold-standard of extirpative resection and carry risk for upper tract tumor recurrence, with reported rates of 23% to 76%.[90] As such, these approaches may yield less optimal results and require multiple additional procedures. Of note, CIS limited to the region within the ureteral orifice. Topical therapies such as BCG along with refluxing ureteral stenting that has been used for in cases of CIS near the ureterovesical junction or transurethral resection of the transmural portion of the ureter for very distal tumors, as an extension of bladder resection procedures, when tumor is limited to the region inside the ureteral orifice and not beyond the bladder wall, thus anatomically managed as bladder cancer.

22. When performing NU or distal ureterectomy, the entire distal ureter including the intramural ureteral tunnel and ureteral orifice should be excised, and the urinary tract should be closed in a watertight fashion. (*Strong Recommendation, Evidence Level: Grade B*)

The management of the ureteral orifice during distal ureterectomy or RNU has been variably described. Traditionally, this aspect of UTUC surgery has been approached as a formal excision of the bladder cuff surrounding the ureteral orifice and entire ureteral tunnel in continuity with the ureter either via a transvesical (e.g., midline cystotomy) or extravesical approach. Depending on surgeon preference and expertise, this aspect of surgery can be approached via minimally invasive (e.g., laparoscopic, robotic-assisted laparoscopic) or open approaches. Others have advocated for a combined endoscopic deep incision surrounding the ureteral orifice or transurethral resection of the ureteral orifice with extravesical traction to complete the excision (the "pluck" technique). The resultant hiatus in the bladder in the location of the excised ureteral orifice with or without the bladder cuff can be closed formally in a watertight fashion in one or more layers; however, delayed closure by secondary intension in a decompressed bladder without formal bladder closure has also been described.

To date, no RCT has compared the different surgical techniques for managing the distal ureter and ureteral orifice during NU or distal ureterectomy for UTUC. This has been studied in retrospective observational studies [114-120] with sample sizes ranging from 84 to 4,266 (total N=12,125), with low ROB in one study,[114] moderate ROB in five studies,[115-117, 119, 120] and high ROB in one study.[118] Two retrospective studies[114, 118] (N=420) demonstrated that formal BCE is associated with improved 5-year OS versus no BCE (71.5% versus 57.0%; p=0.001).[118] In patients undergoing SU for UTUC of the distal ureter (N=84), BCE was independently associated with improved 5-year OS (92.3% versus 73.7%; adjusted HR: 0.31; 95% CI: 0.08 to 1.18).[114]

An association between formal BCE and CSS has been evaluated in seven studies (N=11,478).[114-116, 118-120] BCE was associated with improved CSS versus no BCE in all studies except for two,[115, 117] though some differences were small and/or not statistically significant (Appendix IV). However, in the two largest studies (n=4,266[120] and 4,210[119]), both of which evaluated patients who underwent NU, the adjusted HRs for cancer-specific mortality (CSM) with BCE versus no BCE were 0.88 (95% CI: 0.75 to 1.03)[120] and 0.76 (95% CI: 0.66 to 0.88).[119] Of note, this association was also observed in patients with pT3 (adjusted HR: 0.8; p=0.04), pT4 (adjusted HR: 0.69; p=0.02), and N1-3 disease (adjusted HR: 0.72; p=0.04).[119] Conversely, two studies did not demonstrate a statistically significant association between BCE and CSM.[115,117] There are insufficient data to date documenting associations between BCE and RFS or metastasis-free survival. Limited data demonstrate no significant difference in harms associated with BCE.

There are insufficient data to recommend one surgical approach to the bladder cuff and ureteral orifice over the other. However, to avoid the risk of incomplete resection of the distal ureter and transmural tunnel, the Panel recommends that a clinician should perform a formal BCE with watertight closure of the bladder cuff to avoid urinary extravasation from the bladder, facilitate more rapid catheter removal, and permit instillation of intravesical adjuvant chemotherapy in the perioperative setting.

23. In patients undergoing RNU or SU (including distal ureterectomy) for UTUC, a single dose of perioperative intravesical chemotherapy should be administered in eligible patients to reduce the risk of bladder recurrence. (Strong Recommendation; Evidence Level: Grade A)

Two prospective RCTs have demonstrated that a single instillation of intravesical chemotherapy around the time of NU reduces the risk of subsequent intravesical recurrence of urothelial carcinoma. A phase III trial by O'Brien et al. (ODMIT-C Trial) enrolled 284 patients with no prior history of bladder cancer who were undergoing NU for suspected UTUC to either a single post-operative intravesical dose of mitomycin-C (MMC) or standard management at the time of catheter removal.[121] On the intention-to-treat analysis, 17% of the MMC arm developed a bladder recurrence in the first year compared to 27% in the standard treatment arm (p=0.055). By treatment as per protocol analysis, 17 of 105 patients (16%) in the MMC arm and 31 of 115 patients (27%) in the standard treatment arm developed a recurrence (p=0.03) with no reported serious AEs. A smaller phase II trial by Ito et al. randomized 77 patients to a single intravesical instillation of pirarubicin or standard care

within 48 hours of RNU for UTUC with similar results.[122] As such, the evidence strongly supports the use of single dose of intravesical chemotherapy around the time of RNU to reduce the risk of subsequent bladder recurrence. The exact timing of therapy has varied by study with the ODMIT-C trial instilling intravesical chemotherapy at the time of catheter removal, while other retrospective series reported instillation during surgery or up to 48 hours postoperatively.[121-123]

Numerous agents have been used at the time of trans urethral resection of bladder tumor (TURBT) to reduce the risk of NMIBC recurrence but in the context of UTUC there is little data to support one intravesical chemotherapeutic over another. However, for many clinicians, the recent compelling data supporting the use of a single dose of intravesical gemcitabine at the time of TURBT for NMIBC to reduce the rate of intravesical recurrences combined with concerns about potential chemical peritonitis if there is extravesical extravasation of MMC has led many to convert their practice to the use of gemcitabine rather than MMC.[123, 124] Nevertheless, in the absence of direct comparisons, ultimately the timing of therapy and choice of agent can be modified based on the agent availability and workflow suitable to the clinician.

Lymph Node Dissection (LND)

24. For patients with LR UTUC, clinicians may perform LND at time of NU or ureterectomy. (*Conditional Recommendation; Evidence Level: Grade C*)

Limited evidence exists to support a beneficial role for LND at time of NU or ureterectomy among patients with LR UTUC. To date, no RCT has compared LND versus no LND with respect to impact on oncologic outcomes.

Two recent systematic reviews[125] of observational studies compared LND versus no LND.[126] No statistically significant differences were noted with regard to LND in subsequent oncologic outcomes, including among patients with higher stage tumors. Therefore, the benefit of node dissection among patients with LR UTUC specifically remains unclear. In one study evaluating patients with cN0M0 UTUC (n=7,278) in the SEER database,[127] there was no statistically significant association between lymphadenectomy and OS or CSS in patients with T1 and T2 tumors. Given that most patients with LR UTUC have low-stage tumors on final pathology, while some may be upgraded or upstaged, LND may be considered at time of NU or ureterectomy at the discretion of the clinician according to clinically or radiographically suspicious regional lymphadenopathy or other intraoperative findings suggesting more advanced disease for which nodal staging may be warranted.

25. For patients with HR UTUC, clinicians should perform LND at the time of NU or ureterectomy. (*Strong Recommendation; Evidence Level: Grade B*)

There have been no RCTs to evaluate the effect of LND on oncologic outcomes in patients undergoing NU or SU. Two recent systematic reviews (N=7,516 and N=22,665) of observational studies compared LND with no LND.[125] Findings of the reviews were consistent, with no statistically significant differences in oncologic outcomes, including among patients with higher stage tumors. While studies have attempted to adjust for confounders, the ROB in these studies is substantial, especially as it relates to selection bias: systematic differences in patient baseline characteristics, tumor grade, and tumor stage. Moreover, these studies are unable to confirm the extent or anatomic boundaries of the LND that was performed.

The Panel conducted a re-analysis of some of the studies described in the systematic review by Chan et al.[126] in which hazard ratios were all converted so the comparison was in the same direction (LND versus no LND), to pool data from all studies. In this meta-analysis, LND was associated with better RFS (four studies, HR: 0.58; 95% CI: 0.40 to 0.83) (**Figure 1**).

Two additional recent cohort studies[127, 128] published subsequently also compared LND with no dissection. One study of patients in the National Cancer Database (n=5,905) with clinically localized (≤cT4, N0M0) UTUC found LND was significantly associated with improved OS (adjusted HR: 0.87; 95% CI: 0.78 to 0.96), but worse 90-day mortality (adjusted OR: 1.53; 95% CI 1.03 to 2.27) compared to no LND.[128] The second study evaluated patients with cN0M0 UTUC (n=7,278) in the SEER database.[127] Compared to no LND, the study found performance of a LND was associated with slightly improved OS (adjusted HR: 0.87; 95% CI 0.80 to 0.95) and CSS (adjusted HR: 0.81; 95% CI: 0.73 to 0.95). When patients were stratified according to tumor stage, LND was significantly associated with improved OS in patients with T3 (adjusted HR: 0.88; 95% CI: 0.78 to 0.99) and T4

(adjusted HR: 0.74; 95% CI: 0.59 to 0.94) tumors; while estimates indicated no benefit or were not statistically significant in patients with T1 and T2 tumors. Findings were similar for CSS, with statistically significant benefits in patients with T3 (adjusted HR: 0.83; 95% CI: 0.73 to 0.98) and T4 (adjusted HR: 0.64; 95% CI: 0.47 to 0.88) tumors and non-statistically significant differences in patients with T1 and T2 tumors.

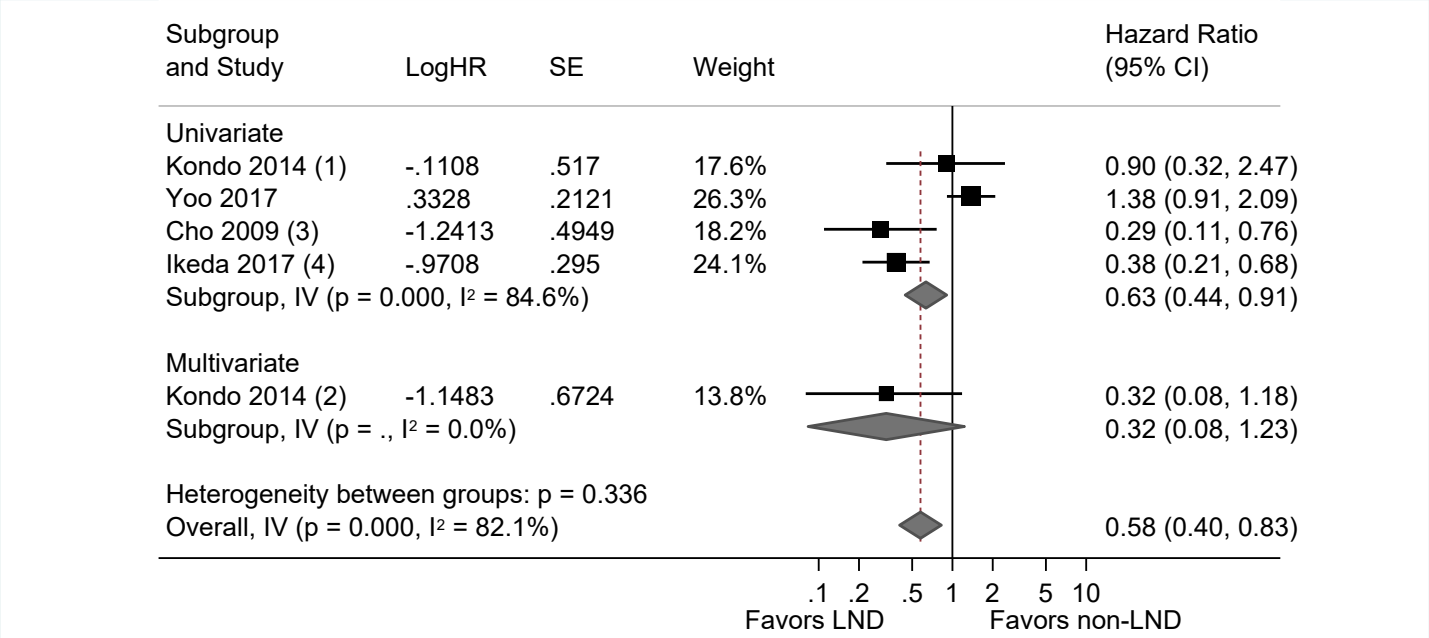
To date, no study has adequately assessed the distribution of lymph node metastases. As such, the appropriate template to yield maximal oncologic outcomes and prognostic information remains to be determined. However, based on anatomic principles, the Panel recommends that the following minimal templates may be considered in most settings of clinically non-metastatic HR disease (cN0M0).

- **Tumors in the pyelocaliceal system**: lymph nodes of the ipsilateral great vessel extending from the renal hilum to at least the inferior mesenteric artery.
- **Tumors in the proximal 2/3 of the ureter**: lymph nodes of the ipsilateral great vessel extending from the renal hilum to the aortic bifurcation.
- **Tumors in the distal 1/3 of the ureter**: ipsilateral pelvic LND to include at minimum the obturator and external iliac nodal packets. Internal and common iliac nodal packets may be removed in the appropriate clinical setting. Limited data suggest cranial migration of lymph node metastases to the ipsilateral great vessels such that higher dissection may be considered in the appropriate clinical setting and per clinician judgement.

Taken in sum, there is sufficient non-randomized evidence to suggest an oncologic benefit to LND at the time of NU for patients with "HR" stratification by guidelines, the Panel recommends LND at the time of NU or SU for patients with HR UTUC.

FIGURE 1: REANALYSIS OF RECURRENCE-FREE SURVIVAL FROM CHAN 2020 SYSTEMATIC REVIEW

(ALL HAZARD RATIOS CONVERTED TO LND VERSUS NO LND)



Notes:
Only included ureteric arm patients with pT2 disease or above and N0M0
Only included renal pelvic arm patients with pT2 disease or above and N0M0
Only included patients with muscle invasive disease and locoregional recurrence
Only included patients with locally advanced UTUC

Neoadjuvant/Adjuvant Chemotherapy and Immunotherapy

26. Clinicians should offer cisplatin-based NAC to patients undergoing RNU or ureterectomy with HR UTUC, particularly in those patients whose post-operative eGFR is expected to be less than 60 mL/min/1.73m^2 or those with other medical comorbidities that would preclude platinum-based chemotherapy in the post-operative setting. (*Strong Recommendation; Evidence Level: Grade B*)

Survival outcomes in patients with HR UTUC after RNU and LND is poor owing to the aggressive nature of the disease and the resulting compromise to renal function that limits further therapeutic options. Optimizing perioperative systemic treatment to improve outcomes is commonly achieved in the neoadjuvant setting when dosing regimens may be better tolerated, allowing more courses to be completed, and permitting patients to proceed to appropriate surgical intervention. Several meta-analyses evaluating NAC for UTUC have identified evidence for improved pathologic outcomes, CSS, and OS with this approach.[129]

Two recently completed NAC trials of cisplatin-based chemotherapy prior to RNU strongly support this position. The designs of these single-arm prospective trials were extrapolated from data in muscle-invasive bladder cancer that provide high level evidence for neoadjuvant cisplatin prior to cystectomy compared to surgery alone.[130, 131] Both trials used selection criteria that predicted for existing muscle-invasive disease at baseline in over 65% of patients.[132] In the ECOG 8141 study, four cycles of NAC with accelerated MVAC (aMVAC, methotrexate, vinblastine, adriamycin, and cisplatin with growth factor support every two weeks) were planned.[133] Eligible patients had HG UTUC of the renal pelvis or ureter, pathologically confirmed and correlated with cross-sectional imaging, were without evidence of locoregional or metastatic disease, and were planned for RNU. In 29/30 aMVAC treated patients, eligibility included ECOG performance status 0 or 1, and creatinine clearance >50 mL/min. The pathologic complete response rate (ypT0N0/Nx) following RNU in this group was 13.8% (90% CI: 4.9-28.8) and deemed worthy of further study. In addition, 62% of eligible treated patients had final pathologic stage of ≤ypT1N0/x, an encouraging endpoint given improved long-term outcomes for patients with non-muscle invasive cancer following NAC in UTUC in retrospective series. Accelerated MVAC was tolerated as expected with 80% of patients completing planned four cycles. No patients progressed prior to surgery, none died of chemotherapy- or surgery-related toxicity. At a median follow-up of 21.1 months, the median relapse-free survival for subjects treated with aMVAC and RNU was not reached.

Renal function outcomes were also evaluated in this trial. Baseline median creatinine clearance was 82 mL/min (53.7 -170) prior to aMVAC with two patients (6.7%) having creatinine clearance < 60 mL/min. Following chemotherapy, 20% had creatinine clearance <60 mL/min, all were still surgery eligible. As expected, the largest decline in renal function occurred post-RNU with 69% having calculated creatinine clearance <60 mL/min. Results from this study have informed the design of EA8192, a randomized phase II/III trial of neoadjuvant aMVAC +/- durvalumab chemotherapy for four neoadjuvant cycles prior to RNU, currently enrolling.

Coleman et al. presented data from a prospective Phase II open label trial in a similar population of patients with HG non-metastatic UTUC planned for RNU, with platinum eligible renal function based on calculated glomerular filtration rate ≥55 mL/ min/1.73m^2 by CKD-EPI.[134] In this fully accrued trial, 58 patients enrolled and were treated with a dosing schedule of split dose cisplatin (35 mg/m^2 on days 1 and 8) with gemcitabine (1,000 mg/m^2 on days 1 and 8) for 4 planned cycles prior to RNU. The study was powered at the 90% level to detect a significant reduction in pathologic stage <ypT2N0 in ≥60% of patients. This trial met its primary endpoint with 63% of patients achieving <ypT2N0 status following surgery, including 19% with complete pathologic response (ypT0N0). Median follow-up was 3.1 years and 2- and 5-year PFS was 78% and 65%, respectively. The 2- and 5-year OS were 93% and 79%, and for both PFS and OS, lower final pathologic stage correlated with better PFS and OS outcomes.

Similar to EA8141, there were no patients with cancer progression post NAC, which precluded surgery, and no treatment related deaths. Further, 89% of patients received at least 3 cycles of NAC, with 47% completing all 4. All patients proceeded to surgery. The strongly

positive data from these phase II trials, the established high-level evidence seen in bladder cancer trials, the consistent findings from pooled meta-analytic data, and the compelling clinical challenges imposed by post-RNU renal function on cis-platinum eligibility support the standard use of NAC regimens for HR UTUC. Observed results seen with phase II trials also set an important benchmark for any future such studies in this disease.

Alternatives to cisplatin-based chemotherapy (i.e., immune checkpoint inhibitors, carboplatin, antibody drug conjugates, targeted FGFR therapies) are not recommended in the neoadjuvant setting (prior RNU or ureterectomy) outside of clinical trials.

27. Clinicians should offer platinum-based adjuvant chemotherapy to patients with advanced pathological stage (pT2–T4 pN0–N3 M0 or pTany N1–3 M0) UTUC after RNU or ureterectomy who have not received neoadjuvant platinum-based therapy. (*Strong Recommendation; Evidence Level: Grade A*)

Adjuvant platinum-based chemotherapy for select patients with UTUC post-RNU is a standard based on results from the randomized phase III POUT trial.[135] In this study, 261 chemotherapy-naïve patients were identified and enrolled post-RNU, with HR patients selected based on postoperative stage in non-metastatic patients of pT2–T4 pN0–N3 M0 or pTany N1–3. In this trial, patients were randomized to platinum chemotherapy day 1 based on eligibility (cisplatin, or carboplatin for glomerular filtration rate <50 mL/min) with gemcitabine days 1 and 8 for four planned adjuvant cycles to start within 90 days of RNU. The trial was designed to show improved disease-free survival (DFS) in the chemotherapy versus the observation arm, and after meeting an early efficacy point, accrual was halted. At a median follow-up of 30.3 months, subjects in the adjuvant chemotherapy arm had improved DFS (HR: 0.45; 95% CI: 0.30 to 0.68; p=0.0001) compared with those on observation. Subjects on the chemotherapy arm had a significantly lower risk of metastases or death compared to observation (HR: 0.48; 95% CI: 0.31 to 0.74; log-rank p=0.0007). Side effects of platinum chemotherapy were as expected with no grade 5 events. The completion rate of four adjuvant cisplatin cycles was low in this dataset at 58%, including 21% of patients who started with cisplatin but switched to carboplatin for post allocation decline in GFR.

A subgroup analysis demonstrated that outcomes for patients with lymph node involvement and those treated with carboplatin chemotherapy were worse than those without positive nodes or treated with cisplatin chemotherapy.[136] As the primary endpoint was powered based on the intent to treat population, speculation about these subgroups, the potential utilization of six versus four cycles for metastatic N+ disease or the impact of carboplatin in this setting are hypothesis generating discussions. Based on these data, carboplatin remains a reasonable choice for HR cisplatin-ineligible patients post-RNU if NAC was not given.

28. Adjuvant nivolumab therapy may be offered to patients who received neoadjuvant platinum-based chemotherapy (ypT2–T4 or ypN+) or who are ineligible for or refuse perioperative cisplatin (pT3, pT4a, or pN+). (*Conditional Recommendation; Evidence Level: Grade B*)

Two completed RCTs compared adjuvant checkpoint inhibitor therapy versus observation (IMvigor 010) or placebo (CheckMate 274) following surgery in patients with HR non-metastatic urothelial carcinoma (Appendix V).[137, 138] Although the majority of patients in these studies underwent radical cystectomy for bladder primaries, 20% of patients in CheckMate 274 and 7% of IMvigor 010 patients underwent surgery for UTUC, with endpoints based on the intention to treat population. Inclusion criteria for both studies were patients with HR urothelial cancer defined as pT3, pT4a, or pN+ for patients who had not received neoadjuvant cisplatin-based chemotherapy and ypT2 to ypT4a or ypN+ for patients who had received neoadjuvant cisplatin.

In the IMvigor 010 trial, (n=406; 29 with UTUC) planned one year of adjuvant atezolizumab did not meet the primary endpoint of improved DFS compared to observation (19.4 months versus 16.6 months; HR: 0.89; 95% CI: 0.74 to 1.08).[139] Another study, the phase III randomized adjuvant study of pembrolizumab in muscle invasive and locally advanced urothelial carcinoma including UTUC patients (AMBASSADOR) versus observation trial, has completed accrual and is maturing with data yet to be presented.[140]

The CheckMate 274 (n=709; 149 with UTUC) study of one year of planned adjuvant nivolumab did meet its co-primary endpoints, with improved DFS (definition per-protocol included within and outside of the urothelial tract)

of 20.8 months (95% CI: 16.5 to 27.6) with nivolumab versus 10.8 months (95% CI: 8.3 to 13.9) with placebo in the intention to treat population.[138] The 6-month DFS benefit of 74.5% with nivolumab and 55.7% with placebo (HR: 0.55; 98.72% CI: 0.35 to 0.85; P<0.001) was even more striking in patients whose tumors expressed PD-L1 (≥1%).

Additionally, non-urothelial tract RFS (77.0% versus 62.7%; HR: 0.72; 95% CI: 0.59 to 0.89), and distant metastasis free survival (MFS, 82.5% versus 69.8%; HR: 0.75; 95% CI: 0.59 to 0.94) were also improved. In a subgroup analysis of patients with UTUC, there was no difference in DFS for renal pelvic cancers (HR: 1.23; 95% CI: 0.67 to 2.23) or the ureter (HR: 1.56; 95% CI: 0.70 to 3.48) in either arm. The small sample size limits the statistical power to detect a difference, and thus the results from this subgroup analysis in UTUC are hypothesis generating only. Based on the strength of the overall evidence, adjuvant nivolumab was approved for UTUC and urothelial carcinoma of the bladder in patients with advanced disease identified from post-surgical pathology findings.

With respect to harms, nivolumab was well tolerated and similar to placebo with respect to overall AEs (98.9% versus 95.4%) and grade 3 or higher AEs (42.7% versus 36.8%).[107] However, nivolumab was associated with increased likelihood of treatment-related AEs (77.5% versus 55.5%) and grade 3 or higher treatment-related AEs (17.9% versus 7.2%). The most common toxicities in the nivolumab group were pruritus (23.1%), fatigue (17.4%), and diarrhea (16.8%); and the most common grade 3 or higher AEs were elevations in serum lipase (5.1%) and amylase (3.7%) levels, diarrhea (0.9%), colitis (0.9%), and pneumonitis (0.9%). Treatment-related death occurred in three patients treated with nivolumab (two due to pneumonitis and one due to bowel perforation). Toxicity-related treatment discontinuation was also higher from nivolumab compared to placebo (12.8% versus 2.0%); most frequently from pneumonitis (1.7%), rash (1.1%), colitis (0.9%), and increased alanine aminotransferase level (0.9%). These toxicities are similar to other checkpoint inhibitor studies with no new safety signals noted. No adjuvant studies have compared nivolumab to platinum-based chemotherapy regimens.

Based on the relative strengths of the available data, the Panel recommends the use of adjuvant platinum-chemotherapy over adjuvant nivolumab for eligible patients who did not receive NAC. Scenarios for use of adjuvant nivolumab include: 1) patients with contraindications to platinum-based chemotherapy (e.g., poor renal function, performance status, sensorineural hearing loss, neuropathy or congestive heart failure, allergy), 2) patients with HR pathology after NAC, 3) patients who refuse standard forms of adjuvant chemotherapy after appropriate counseling.

29. In patients with metastatic (M+) UTUC, RNU or ureterectomy should not be offered as initial therapy. (*Expert Opinion*)

No clear evidence supports upfront RNU without chemotherapy in the setting of known metastatic (M+) UTUC. Oncologic outcomes in the metastatic setting are strongly determined by response to systemic therapy, and surgical treatment has no demonstrable therapeutic efficacy for cytoreduction or as a single modality in this setting. Potential harms such as delay or inability to receive systemic therapy due to consequences of surgery can significantly and negatively impact oncologic outcomes and OS in this setting. Therefore, clinicians should favor systemic therapy and alternative approaches (i.e., radiotherapy with or without chemotherapy in selected cases) for inoperable or symptomatic patients with M+ UTUC.

Retrospective studies suggesting clinical benefit from surgery to the primary site in patients with metastatic UTUC apply specifically to those who have already received first-line chemotherapy or from data sets where use of peri-operative chemotherapy is poorly documented, thus limiting interpretation and applicability due to strong selection biases and significant weaknesses in the data sets.[141, 142]

30. Patients with clinical, regional node-positive (cN1-3, M0) UTUC should initially be treated with systemic therapy. Consolidative RNU or ureterectomy with lymph-node dissection may be performed in those with a partial or complete response. (*Expert Opinion*)

The Panel emphasizes that, in the case of cN1-3 UTUC, the primary treatment is chemotherapy, and that surgery with curative intent be considered as a consolidation strategy after complete or, in select cases, partial response. Supporting data for this statement are derived

mainly from studies of platinum-based chemotherapy regimens, and results should be interpreted contextually.

Patients with clinically suspicious lymph nodes are classified as HR unfavorable with likely established locally advanced or metastatic disease. These patients with clinically evident or biopsy proven regional nodal metastases who demonstrate suitable response to systemic therapy that converts their disease to a clinical state amenable to surgical resection should be offered surgical treatment if medically suitable. Pooled data from comparative outcomes utilizing NAC in patients with clinically node positive (cN+) disease supports this approach.

Three reviews included up to six individual studies were consistent in finding NAC associated with improved oncologic outcomes versus NU alone. The largest total sample (N=1,252) included a study of patients with cN+ M0 UTUC in the U.S. National Cancer Database (n=720).[143] Based on a pooled analysis of adjusted risk estimates, NAC was associated with significantly better OS (5 studies; adjusted HR: 0.53; 95% CI: 0.40 to 0.69) and CSS (2 studies; adjusted HR: 0.39; 95% CI: 0.23 to 0.67) compared to NU alone. Findings for OS were similar in the subgroup of patients with locally advanced tumors (≥cT3 or cN+; 4 studies; adjusted HR: 0.54; 95% CI: 0.41 to 0.72; p<0.001). A review including 5 studies common to all the reviews also found NAC associated with improved RFS versus NU (3 studies; HR 0.50; 95% CI: 0.37 to 0.66; p<0.0001).

31. **Patients with unresectable UTUC (including those who are ineligible or refuse surgery [RNU or ureterectomy]) should be offered a clinical trial or best supportive care including palliative management (radiation, systemic approach, endoscopic, or ablative) for refractory symptoms such as hematuria. (*Expert Opinion*)**

Patients' localized disease may be deemed unresectable or ineligible for extirpative surgical management due to significant medical comorbidities or other factors including refusal to accept surgical treatment (e.g., solitary kidney). Formulating alternative care options should be approached with multi-disciplinary input with a focus on realistic goals of care such as providing means of local control for functional preservation (e.g., renal function) and palliation (e.g., bleeding, infection). Appropriate patient counseling with an explanation of goals and expectations should be provided and documented. Clinical trials, where available, should be discussed with, sought out, and offered to eligible patients. Multi-modal approaches include combination of endoscopic management to maintain upper and lower tract function (e.g., stents, nephrostomies, ablation for bleeding and local control) in addition to systemic treatment options if available. Rarely, radiation, angioembolization, or percutaneous ablation for palliation of bleeding can be offered based on anecdotal case report data.[144-146]

SURVEILLANCE AND SURVIVORSHIP

Post-Treatment Surveillance

Surveillance After Kidney Sparing

32. **Low-risk patients managed with kidney sparing treatment should undergo a follow-up cystoscopy and upper tract endoscopy within one to three months to confirm successful treatment. Once confirmed, these patients should undergo continued cystoscopic surveillance of the bladder at least every six to nine months for the first two years and then at least annually thereafter. Endoscopy should be repeated at six months and one year. Upper tract imaging should be performed at least every six to nine months for two years, then annually up to five years. surveillance after five years in the absence of recurrence should be based on shared decision-making between the patient and clinician. (*Expert Opinion)***

Surveillance regimen should be tailored to disease risk as well as treatment modalities taken.

Patients with LG (LR) UTUC managed with nephron-sparing approaches should, at a minimum, undergo cystoscopic surveillance three months after endoscopic treatment, then once again within the first year after treatment, then every six to nine months for two years. Upper tract imaging, preferably with CT urogram, should be done at least every six to nine months for the first several years but can then be done annually out to year five. Follow-up ureteroscopic evaluation should be performed at a regular interval within the first year but can then be performed with any symptoms or significant findings on upper tract imaging.

Risk of recurrence

Endoscopy and radiographic imaging can be utilized to evaluate the upper tracts for recurrence within the affected and contralateral system. Although risk of recurrence varies on disease characteristics as well as medical therapy (e.g., mitomycin gel), periodic evaluation will diagnose disease earlier in the disease progression. Of three studies that reported adjusted risk estimates, one study (n=120) found endoscopic management associated with increased risk of any (local, intravesical, or distant) recurrence (adjusted HR: 3.56; 95% CI: 1.73 to 7.35),[84] one study found endoscopic management associated with improved intravesical RFS (adjusted HR: 0.56; 95% CI: 0.25 to 1.25),[81] and one study found endoscopic management associated with increased risk of local recurrence (adjusted HR: 1.27; p=0.001) but no difference in risk of intravesical RFS (adjusted HR: 0.90; p=0.52).[86] The follow-up evaluation schedule attempts to balance the morbidity and cost of follow-up with the risk of disease recurrence. Clinicians may elect to increase the intensity of surveillance above the minimum recommendations as listed in the guideline according to their assessment of an individual patient's risk and shared decision-making.

Risk of metastasis

Another important reason for disease follow-up is to evaluate patients for metastatic disease; the likelihood of which for LG/LR disease is low. Three studies reported inconsistent results for metastasis: one study[82] (n=162) reported higher MFS for patients with LG UTUC who underwent ureteroscopic management versus patients with any grade UTUC who underwent NU (5-year MFS 84% versus 60%; 10-year MFS 75% versus 54%), one study[64] (n=453) reported similar 5-year MFS for patients with LG UTUC who underwent endoscopic management versus NU (81% versus 84%, p=0.99), and one study[84] (n=120) that did not stratify results by UTUC grade reported similar likelihood of distant metastasis for endoscopic management versus NU (24% versus 27%).

In an asymptomatic patient with a history of LR UTUC, a clinician should perform baseline chest imaging, which can be done by chest X-ray or CT of the chest, but routine imaging thereafter is not required.

33. High-risk patients managed with kidney sparing treatment should undergo a follow-up cystoscopy and upper tract endoscopy with cytology within one to three months. Patients with no evidence of disease should undergo cystoscopic surveillance of the bladder and cytology at least every three to six months for the first three years and then at least annually thereafter. Endoscopy should be repeated at least at six months and one year. Upper tract imaging should be performed every three to six months for three years, then annually up to five years. surveillance after five years in the absence of recurrence should be encouraged and based on shared decision-making between the patient and clinician. (*Expert Opinion*)

Surveillance regimen should be tailored to disease risk as well as treatment modalities received.

Some patients with HGT1 or less (HG Ta, T1, or CIS) may be managed with nephron-sparing treatments, such as endoscopic management, topical therapy, segmental ureteral resection (including distal ureterectomy) or other therapies (e.g., systemic therapy or surveillance). Patients with HG Ta, T1, or CIS urothelial carcinoma receiving nephron-sparing treatment should undergo cystoscopic surveillance starting within three months after treatment, continuing every 3-6 months for 3 years, and then every 6-12 months through year 5. Follow-up ureteroscopy should be performed at least once within three to six months of endoscopic therapy and subsequently at the discretion of the clinician. Ureteroscopy for patients who undergo definitive surgical management (e.g., SU or distal ureterectomy) should be performed at three to six months after resection, and then may be performed at the discretion of the clinician, who might prefer cross-sectional excretory imaging in lieu of ureteroscopy. For patients with HGT1 or less, managed by nephron-sparing treatment, upper tract imaging with CT urogram and basic metabolic panel (BMP) should be performed every 3-6 months for 3 years, then every 6-12 months for 2 years, and annually thereafter. Chest imaging with chest X-ray or CT of the chest is recommended every 6-12 months to evaluate for intrathoracic metastasis up to 5 years following last diagnosis/treatment. As discussed with respect to the initial characterization of UTUC, MR urography or retrograde pyelography combined with non-contrast axial

imaging may be utilized in patients in whom the administration of iodinated contrast is contraindicated.

Risk of recurrence

The majority of studies evaluating risk of recurrence with nephron-sparing treatment are retrospective heterogeneous analyses that include both LG and HG tumors. A retrospective cohort study of 198 patients with pTa, pTis, or pT1 disease received either endoscopic treatment or RNU, of whom 15% and 25% had HG disease, respectively.[42] Mean postoperative creatinine levels were slightly improved among patients who received nephron-sparing surgery (1.32 standard deviation 0.47] versus 1.64 [SD 0.79; p=0.048]). Among patients receiving endoscopic treatment, recurrence within the ipsilateral upper urinary tract was higher (25% versus 1.2%; p<0.001), but recurrence in the bladder was slightly lower (15% versus 36%; p=0.056). A smaller retrospective cohort of 43 patients undergoing either endoscopic treatment or RNU, of whom 20% and 91% had HG disease, respectively, showed a higher rate of bladder recurrence among patients undergoing nephron-sparing surgery (60% versus 18%; p=0.008).[40] Given the HR of recurrence in both the upper and lower urinary tract, risk-adapted surveillance suggests close monitoring to reflect a high recurrence risk within this patient population.

Risk of metastasis

In studies comparing endoscopic management versus NU, few patients undergoing endoscopic management had HG UTUC, and most patients received nephron-sparing treatment did so under palliative or emergent conditions (e.g., bleeding, renal failure).[82] In one study, ureteroscopic management for HG UTUC in 14 patients was associated with worse 2-year OS (54% versus 77%), CSS (54% versus 78%), and MFS (34% versus 66%) versus NU in 80 patients (any grade; 71% with HG UTUC). At 5 years, survival was 0% in the HG ureteroscopy group, compared with 5-year OS of 58%, CSS of 64%, and MFS of 60% with surgery. One other study found percutaneous endoscopic management associated with worse OS (34.6 months versus 58.0 months) and CSS (27.8 months versus 56.7 months) in the subgroup patients with grade 3 UTUC (n=34).[83] In another retrospective cohort of 8,304 patients, 633 patients underwent nephron-sparing treatment of whom 39.7% had HG disease. Median OS and 3-year DSS were worse among those undergoing nephron-sparing treatment compared to those undergoing NU (1.9 years versus 7.8 years; p<0.001 and 73.7% versus 92.4%; p<0.001; respectively).[58] Given the comparatively worse OS, CSS, and MFS rates among patients with HG disease undergoing nephron-sparing surgery, a risk-adapted surveillance scheme should incorporate cross-sectional imaging of the abdomen and pelvis as well as chest imaging to evaluate sites of metastasis.

34. **Patients who develop urothelial recurrence in the bladder or urethra or positive cytology following treatment for UTUC should be evaluated for possible ipsilateral recurrence or development of new contralateral upper tract disease. (*Expert Opinion*)**

The development of a recurrence of urothelial carcinoma in the lower urinary tract or a positive cytology in the context of a patient with a history of UTUC should raise the possibility of recurrent disease in the upper tracts. Thus, patients who develop lower tract recurrence or a positive cytology without a clear etiology should undergo an evaluation of the upper tracts. Depending on the clinical scenario this may be via cross-sectional imaging or retrograde pyelography with or without selective upper tract cytology. If these modalities suggest the presence of upper tract involvement, then further evaluation, including endoscopy, is warranted.

Surveillance after Radical NU

35. **After NU, patients with <pT2 N0/M0 disease should undergo surveillance with cystoscopy and cytology within three months after surgery, then repeated based on pathologic grade. For LG this should repeated at least every six to nine months for the first two years and then at least annually thereafter. For HG, this should be repeated at least every three to six months for the first three years and then at least annually thereafter. Due to the metastasis risk and estimated 5% probability for contralateral disease, cross-sectional imaging of the abdomen and pelvis should be done within 6 months after surgery and then at least annually for a minimum of 5 years. Surveillance after five years in the absence of recurrence should be encouraged and based on shared decision-making between the patient and clinician (See Table 6). (*Expert Opinion*)**

Follow up after NU for patients with non-muscle invasive, node-negative UTUC should be largely focused on the risk of intravesical recurrence. Two systematic reviews of recurrence rates after NU found similar rates of intravesical recurrence after NU to be approximately 29% with a median time to recurrence of 6-12 months[147] or 22 months.[148] The study by Kapoor et al. also summarized the overall risk of recurrence to the contralateral upper tract at 2.2% (range 0% to 4.6%; mean follow-up 46.7 months).[147] Locke et al. led a large Canadian study of over a 1,000 patients that found similar results with a local recurrence rate (both bladder and upper tract) of 24% with a median time to recurrence of 7 months.[149] That study also noted that 91% of the local recurrences were identified within the first 2 years, while late recurrences did occur as late as 150 months after surgery. Therefore, in the first two years after NU, there should be regular attention paid to monitoring for intravesical recurrence through regular cystoscopic surveillance. After two years, the frequency can be significantly reduced though, as with non-muscle invasive bladder cancer, how long surveillance should be continued is not clear.[150] Periodic imaging of the upper tracts should be undertaken given the risk of recurrence to the contralateral upper tract, preferably with cross-sectional imaging such as CT urogram, though the rate is low enough that this can be done annually after NU.

The Locke et al. study broke down the risk of regional or distant recurrence by grade and stage when examining the risk of locoregional or distant metastases.[149] Patients with less than pT2 or pN+ disease were considered either LR (pTa-T1, pN0, LG, no LVI, and not multifocal) or intermediate (pTa-T1, pN0 and HG, LVI present, or multifocal). The 3-year estimated freedom from regional or distant metastases were 93% and 87% for these low- and intermediate-risk groups, respectively. The rate of intrabdominal recurrences in LR patients from this study was very low while in intermediate-risk patients it was 17%, with most occurring within the first 2 years. Thus, periodic imaging of the abdomen and pelvis is warranted, especially for those HG disease, LVI or tumor multifocality, particularly for the first two years. The risk of lung metastases for patients with less than pT2 or pN+ disease is overall low but can occur in those with HG disease so periodic chest imaging (**Table 6**) should be undertaken and can be done via chest x-ray or CT of the chest, though the former is likely sufficient, less costly, and associated with less radiation exposure.

T2+ MANAGED WITH NU

36. For Patients who have undergone NU for ≥pT2 Nx/0 disease, a clinician should perform surveillance cystoscopy with cytology at three months after surgery, then every three to six months for 3 years, and then annually thereafter. Cross-sectional imaging of the abdomen and pelvis with multiphasic contrast-enhanced CT urography should be performed every three to six months for years one and two, every six months at year three, and annually thereafter to year five. A clinician should perform chest imaging, preferably with chest CT, every 6-12 months for the first 5 years. Beyond five years after surgery in patients without recurrence, ongoing surveillance with cystoscopy and upper tract imaging may be continued on an annual basis according to principles of shared/informed decision-making. (*Expert Opinion*)

Regional Recurrences (Bladder) following NU

Follow-up after NU for non-metastatic node-negative pT2 and higher disease requires surveillance for local and regional recurrence, intravesical recurrences, and distant metastases. A meta-analysis of 59 studies[147] evaluating recurrences following NU reported a 29% risk of intravesical recurrence within a median 6-12 months after RNU. A 2016 systematic review of 18 studies enumerated key risk factors for intravesical recurrence including male sex (HR: 1.37; p<0.001), previous bladder cancer (HR: 1.96; p<0.001), preoperative CKD (HR: 1.87; p=0.002), positive preoperative urinary cytology (HR: 1.56; p<0.001), ureteral tumor site (HR: 1.27, p<0.001), multifocality (HR: 1.61; p=0.002), invasive pathologic T-stage (HR: 1.38; p<0.001), presence of necrosis (HR: 2.17; p=0.02), laparoscopic approach (HR: 1.62; p=0.003), extravesical bladder cuff removal (HR: 1.22; p=0.02), and positive surgical margins (HR 1.90; p=0.004).[148] Additional independent risk factors for intravesical recurrence included having positive surgical margins (HR: 3.36; 95% CI: 1.36 to 8.33) and prior ureteroscopic biopsy (HR: 1.39; 95% CI: 0.88 to 2.19).[151]

TABLE 6: SURVEILLANCE AFTER COMPLETE TREATMENT

The following surveillance schedules are recommended in the setting of complete treatment where no residual or recurrent tumor is identified or clinically suspected. Earlier intervals of follow-up endoscopy may be used in cases of concern for incomplete treatment (e.g., larger tumors, more difficult access, poor visibility, disease biology). The Panel recognizes the limitations of the data on tumor recurrence and optimal intervals of follow-up which require further study. Any clinical findings of new or worsening disease should prompt re-evaluation.

Year		1				2				3				4				5				
Month	0	3	6	9	12	15	18	21	24	27	30	33	36	39	42	45	48	51	54	57	60	>60 months
Kidney-Sparing, Low-Risk																						
Cystoscopy, Cytology	-	X	X	-	X	-	X	-	X	-	-	-	X	-	-	-	X	-	-	-	X	-
Upper Tract Endoscopy	-	X	X	-	X	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
Cross-Sectional Imaging*	-	X	-	-	X	-	X	-	X	-	-	-	X	-	-	-	X	-	-	-	X	-
Chest Imaging	-	-	-	-	X	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
BMP	-	-	-	-	X	-	-	-	X	-	-	-	X	-	-	-	X	-	-	-	X	-
Kidney-Sparing, High-Risk																						
Cystoscopy, Cytology	-	X	X	-	X	-	X	-	X	-	X	-	X	-	-	-	X	-	-	-	X	O
Upper Tract Endoscopy	-	X	X	-	X	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
Cross-Sectional Imaging*	-	X	X	-	X	-	X	-	X	-	X	-	X	-	-	-	X	-	-	-	X	O
Chest Imaging	-	-	X	-	X	-	X	-	X	-	-	-	X	-	-	-	-	-	-	-	-	-
BMP	-	-	-	-	X	-	-	-	X	-	-	-	X	-	-	-	X	-	-	-	X	-
Post Nephroureterectomy, <pT2, N0/NX																						
Cystoscopy, Cytology	-	X	X	O	X	-	X	-	X	-	-	-	X	-	-	-	X	-	-	-	X	-
Cross-Sectional Imaging*	-	-	X	-	X	-	-	-	X	-	-	-	X	-	-	-	O	-	-	-	O	-
Chest Imaging	-	-	-	-	X	-	-	-	-	-	-	-	-	-	-	-		-	-	-		-
BMP	-	X	-	-	X	-	-	-	X	-	-	-	X	-	-	-	X	-	-	-	X	-
Post Nephroureterectomy, ≥pT2																						
Cystoscopy, Cytology	-	X	X	-	X	-	X	-	X	-	X	-	X	-	-	-	X	-	-	-	X	O
Cross-Sectional Imaging*	-	X	X	-	X	-	X	-	X	-	-	-	X	-	-	-	X	-	-	-	X	O
Chest Imaging	-	X	X	-	X	-	X	-	X	-	-	-	X	-	-	-	X	-	-	-	X	-
BMP	-	X	-	-	X	-	-	-	X	-	-	-	X	-	-	-	X	-	-	-	X	-

* Cross-sectional imaging of the abdomen and pelvis with CT or MRI should be performed with contrast when possible

X	Recommended	(Should be performed in the associated time interval)
O	Optional	(May be performed in the associated time interval)
-	As indicated	(Performed in the associated time interval for clinical indications)

A large Canadian study (n=1,029) similarly identified a 26% risk of urothelial (bladder or contralateral upper tract) recurrence with a mean time to recurrence of 7 months.[149] Post-NU bladder recurrences were observed in 21%, 26%, and 36% of patients with UTUC of the renal pelvis, ureter, or both, respectively. In patients with HR disease, defined as ≥pT2 or pN+ and any grade, with or without LVI or multifocality, bladder recurrences were observed in 53% of patients compared to 14% and 33% for low- and intermediate-risk disease; with 52% of recurrences in the bladder in the intermediate-risk categories occurring in the first year following NU. There are conflicting data regarding the risk of bladder recurrence according to the location of the primary tumor. Given the substantial risk of local (bladder) recurrences within the first years following NU, risk adapted surveillance with cystoscopy and urine cytology at routine intervals is indicated to facilitate prompt detection of bladder recurrences.

Locoregional recurrence, retroperitoneal nodal and distant metastases following NU

In the previously mentioned meta-analysis of 59 studies[147] evaluating recurrences following NU, in addition to the risk of intravesical recurrence, they

reported recurrences of the retroperitoneum or pelvis occurred in 4.6% of patients within an average 32.7 months, and distant metastases occurred in 16.4% within an average of 46.8 months. Retroperitoneal lymph node metastasis occurred in 5.2% of patients within a mean of 46.8 months), while lung, liver, and bone metastases were observed in 4.8%, 4.1%, and 3.7% of patients, respectively. The median time to metastases was 13months to 16 months (range 1 month to 50 months postoperatively). The large Canadian study (n=1,029) mentioned previously found 24% of patients experience locoregional (in the nephrectomy bed or retroperitoneal lymph nodes) or distant (lung, bone, liver, brain, or other) recurrence with a mean time to recurrence of 8 months.[149] In this analysis, 91% of local recurrences were diagnosed in the first 2 years, though late local recurrences (up to 150 months) were observed. Post-NU locoregional and distant recurrences were observed in 21%, 24%, and 31%, respectively. In patients with intermediate- and HR UTUC, while rare, the vast majority of recurrences to the nephrectomy bed, liver, and distant metastases to the lungs and bones were observed in patients with intermediate- and HR disease within 18-24 months following NU. Risk factors for recurrence following NU include risk factors associated with increased risk of recurrence were multifocality, stage T3-4, grade G3, and presence of lymph node metastasis; UTUC site in ureter versus renal pelvis was not an independent predictor.[152] Given this risk of locoregional recurrence and metastasis in patients with $\geq$ pT2 UTUC following NU, risk-adapted routine surveillance with contrast-enhanced cross-sectional imaging and urography is recommended, with decreasing intensity in years three to five, and subsequent follow-up surveillance recommended according to principles of informed/shared decision-making.

Of note, brain metastases are rare following NU, but have been observed only in patients with a prior history of HR UTUC, within an average of 18 months of NU.[147] Patients undergoing follow-up for HR UTUC following NU with acute neurological signs or symptoms should undergo prompt neurologic evaluation with cross-sectional imaging of the brain and/or spine by CT or MRI.

For patients undergoing follow-up for treated UTUC, additional site-specific imaging can be ordered as warranted according to clinical symptoms suggestive of local recurrence or metastatic spread. PET scans should not be obtained routinely but may be selectively considered for patients who are at risk for metastatic recurrence and are not able to have contrast enhanced CT and MRI. Finally, patients with findings suggestive of metastatic UTUC should be evaluated to define the extent of disease and referred to medical oncology for further management.

In addition to following patients for cancer recurrence or metastasis, clinicians should monitor patients for the sequelae of NU. Following NU for HR UTUC, the Panel recommends that patients should undergo periodic laboratory assessment including serum creatinine level, eGFR, and urinalysis. Other laboratory evaluations (e.g., CBC, LDH, liver function tests, and alkaline phosphatase) may be obtained at the discretion of the clinician or if advanced disease is suspected. In patients who develop progressive renal insufficiency or proteinuria should be referred to nephrology.

Survivorship

37. For patients with reduced or deteriorating renal function following NU or other intervention, clinicians should consider referral to nephrology. (*Expert Opinion*)

Referral to nephrology should be considered for patients with eGFR less than 45 mL/min/1.73m^2, confirmed proteinuria, diabetics with preexisting CKD, or whenever eGFR is expected to be less than 30 mL/min/1.73m^2 after intervention.

The long-term impact of renal dysfunction increases risks of osteoporosis, anemia, metabolic and cardiovascular disease, hospitalization and death. Effective treatment strategies are available to slow the progression of CKD and reduce cardiovascular risks, and therefore timely identification of progressive renal dysfunction and/or proteinuria can provide opportunity for medical intervention when indicated. The two formulas for monitoring eGFR commonly reported in the contemporary literature at this time are the Modification of Diet in Renal Disease and CKD – Epidemiology Collaboration (CKD-EPI) equations.

38. Clinicians should discuss disease-related stresses and risk factors and encourage patients with urothelial cancer to adopt healthy lifestyle habits, including smoking cessation, exercise,

and a healthy diet, to promote long-term health benefits and quality of life. (*Expert Opinion*)

Risk factors such as smoking are associated with advanced disease stage, recurrence and worse CSM among patients with UTUC, with the highest risk among current smokers.[153] Therefore, clinicians should discuss and facilitate smoking cessation with patients at the time of diagnosis and treatment. UTUC is also associated with metabolic syndrome and obesity, with obesity adversely impacting disease-specific outcomes among patients undergoing RNU.[154, 155] Clinicians should, therefore, encourage patients to adopt healthy lifestyle habits regarding exercise and a healthy diet to promote long-term health benefits and quality of life. Finally, clinicians should work with patients and their primary care providers to ensure that comorbidities are optimally managed throughout the course of care for UTUC and during surveillance to maximize quality of life during survivorship.

Future Directions

Urothelial cancers can arise anywhere in the urinary tract and anatomical features can affect management. Techniques and approaches for addressing tumors in the lower urinary tract (bladder and urethra) have several advantages for standardizing management strategies since they are more easily accessed, clinically staged, locally treated, and readily followed than tumors arising in the upper tract. The large variety of clinical scenarios encountered in upper tract disease coupled with limited access and instrumentation as well as risks of significant comorbidities and organ dysfunction present major challenges and barriers to management that are only recently being recognized and confronted through concerted collaborative efforts required in this rare disease. This last feature also underscores the most serious unmet need that this guideline seeks to address, which are the large education gaps and variation in clinical care surrounding a highly lethal malignancy, rarer than testis cancer, with concentrated expertise in few dedicated centers. Educating clinicians about the current state of medical knowledge, highlighting important nuances of management, and teaching specialized techniques necessary for safe and successful treatment is a pressing priority.

Biology and Biomarkers

There is no one-size-fits-all approach to treating UTUC, and further refinements are needed for characterizing aspects of disease risk and biology to help direct care. Recent studies have identified significant genomic distinctions between primary UTUC and primary bladder cancers, namely a higher prevalence of activating FGFR3 mutations (fibroblast growth factor receptor 3) in UTUC as a key driver for tumorigenesis. Investigating the key question as to why this occurs more in upper tract tumors may help lead toward identifying causative factors and the development of preventative strategies, particularly in HR populations such as LS. Genomic markers may also prove useful as less non-invasive biomarkers of tumor grade and stage and for identifying potential pathways for directed treatment, such as FGFR3 inhibition. Other urinary biomarkers investigated to identify UTUC have suggested improved accuracy over urinary cytology, such as DNA methylation assays, RNA panels and cell-free DNA.[156-160] Further evaluation of these panels in the clinically relevant setting of screening, evaluation and surveillance seem warranted. Enhancing diagnostic capabilities utilizing the limited tissue samples yielded in UTUC would improve risk stratification and refine treatment planning while facilitating less invasive follow-up approaches to monitor for recurrence or response to treatment. Like surveillance for lower tract disease, urinary biomarkers may provide a less invasive and easily accessible means to refine post-treatment follow-up for urothelial recurrence with better-informed indications and timing for endoscopic surveillance procedures.

Instrumentation and Ablative Treatments

Improvements in flexible digital endoscopes have greatly improved visualization and access to the upper urinary tract to reach and identify tumors. Instrumentation to allow for effective and safe tissue sampling has been much slower to develop – leaving clinicians to struggle using techniques that are highly skill-dependent and inefficient. Newer devices are in development that may leverage the ability of robotic endoscopy with snake-like instruments to offer better and more precise endoscopic surgical capabilities. The advent of new therapies such as reverse thermo-hydrogel preparation of mitomycin have provided an important new means of treating low-risk tumors. Additional treatments to support kidney sparing approaches are yet needed, especially for small volume HG cancers. Energy devices such as the thulium:YAG laser have recently been approved and added to thermal

ablative capabilities. New photodynamic treatments are also now in Phase III clinical trials to offer additional options for treatment. While these primary treatment options have great therapeutic potential, urothelial recurrences are a subsequent issue in follow-up which other groups are also addressing through clinical trials using approaches such as instilled topical chemotherapeutics.

Multi-Disciplinary Care

Managing patients with UTUC requires a multi-disciplinary team approach to optimize overall care. Access to medical genetics specialists is important for screening and counseling patients with LS – a population just beginning to be recognized and gain appropriate attention for the challenges in care. Improvements in surgical management have limits when disease biology exceeds localized treatment requiring systemic therapies. The integration of medical oncology expertise is therefore critical to provide risk-appropriate adjunctive care to improve cancer specific outcomes and quality of life. Clinical trials with close collaboration between medical oncologist and urologist are addressing some of the key issues of multi-disciplinary care and listed below. The developing field of nephro-oncology also plays a significant role in treatment planning for these vulnerable patient populations who face the prospect of severe renal functional decline and require special attention. Partnerships among these specialties are developing in centers with dedicated UTUC programs to centralize and standardize care – a strategy that has proven effective in optimizing outcomes for other rare cancers that are prone to mismanagement.

Abbreviations

AE	Adverse Event
ASCO	American Society of Clinical Oncology
AUA	American Urological Association
AUAER	American Urological Association Education and Research
BCG	Bacillus Calmette–Guérin
BMP	Basic Metabolic Panel
BCE	Bladder Cuff Excision
BOD	Board of Directors
CSS	Cancer-Specific Survival
CSM	Cancer-Specific Mortality
CIS	Carcinoma in Situ
CDC	Centers for Disease Control and Prevention
CKD	Chronic Kidney Disease
CRC	Colorectal Cancers
CT	Computerized Tomography
CI	Confidence Interval
DM	Diabetes Mellitus
DFS	Disease-Free Survival
ESRD	End-Stage Renal Disease
eGFR	Estimated Glomerular Filtration Rate
FNA	Fine-Needle Aspiration
FISH	Fluorescence In Situ Hybridization
HNPCC	Hereditary Nonpolyposis Colorectal Cancer
HG	High-Grade
HR	High-Risk
HS	High-Stage
HTN	Hypertension
IHC	Immunohistochemical
LG	Low-Grade
LR	Low-Risk
LND	Lymph Node Dissection
LVI	Lymphovascular Invasion
LS	Lynch Syndrome
MR	Magnetic resonance
MMR	Mechanisms of Mismatch Repair
MSI	Microsatellite Instability
MMC	Mitomycin-C
MDCTU	Multidetector Computed Tomography Urography
NCCN	National Comprehensive Cancer Network
NPV	Negative Predictive Value
NAC	Neoadjuvant Chemotherapy
NU	Nephroureterectomy
OHSU	Oregon Health & Science University
OS	Overall Survival
PPV	Positive Predictive Value
PGC	Practice Guidelines Committee
PFS	Progression-Free Survival
RNU	Radical Nephroureterectomy
RCT	Randomized Control Trial
RFS	Recurrence-Free Survival
ROB	Risk of Bias
SQC	Science and Quality Council
SU	Segmental Ureterectomy
SEER	Surveillance, Epidemiology, and End Results
TURBT	Trans Urethral Resection of Bladder Tumor
US	Ultrasound
UTUC	Upper Tract Urothelial Cancer

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DISCLAIMER

This document was written by the Upper Tract Urothelial Carcinoma Panel of the American Urological Association Education and Research, Inc., which was created in 2021. The Practice Guidelines Committee (PGC) of the AUA selected the Panel Chair. Panel members were selected by the Panel and PGC Chair.

Membership of the panel included specialists with specific expertise on this disorder. The mission of the panel was to develop recommendations that are analysis-based or consensus-based, depending on panel processes and available data, for optimal clinical practices in the early detection of prostate cancer setting.

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While these guidelines do not necessarily establish the standard of care, AUA seeks to recommend and to encourage compliance by practitioners with current best practices related to the condition being treated. As medical knowledge expands and technology advances, the guidelines will change. Today these evidence-based guidelines statements represent not absolute mandates but provisional proposals for treatment under the specific conditions described in each document. For all these reasons, the guidelines do not pre-empt physician judgment in individual cases.

Treating physicians must take into account variations in resources, and patient tolerances, needs, and preferences. Conformance with any clinical guideline does not guarantee a successful outcome. The guideline text may include information or recommendations about certain drug uses (“off label”) that are not approved by the Food and Drug Administration (FDA), or about medications or substances not subject to the FDA approval process. AUA urges strict compliance with all government regulations and protocols for prescription and use of these substances. The physician is encouraged to carefully follow all available prescribing information about indications, contraindications, precautions and warnings. These guidelines and best practice statements are not intended to provide legal advice about use and misuse of these substances.

Although guidelines are intended to encourage best practices and potentially encompass available technologies with sufficient data as of close of the literature review, they are necessarily time-limited. Guidelines cannot include evaluation of all data on emerging technologies or management, including those that are FDA-approved, which may immediately come to represent accepted clinical practices.

For this reason, the AUA does not regard technologies or management that are too new to be addressed by this guideline as necessarily experimental or investigational.

References

1. Green DA, Rink M, Xylinas E et al: Urothelial carcinoma of the bladder and the upper tract: Disparate twins. J Urol 2013; **189:** 1214.
2. Audenet F, Isharwal S, Cha EK et al: Clonal relatedness and mutational differences between upper tract and bladder urothelial carcinoma. Clin Cancer Res 2019; **25:** 967.
3. SEER: Renal pelvis

seer 5-year relative survival rates, 2012-2018. 2018 Published. Available at: https://seer.cancer.gov/statistics-network/explorer/application.html?site=640&data_type=4&graph_type=5&compareBy=sex&chk_sex_1=1&chk_sex_3=3&chk_sex_2=2&series=9&race=1&age_range=1&stage=101&advopt_precision=1&advopt_show_ci=on&hdn_view=0&advopt_display=2#graphArea

4. Harris RP, Helfand M, Woolf SH et al: Current methods of the us preventive services task force: A review of the process. Am J Prev Med 2001; **20:** 21.
5. Shea BJ, Reeves BC, Wells G et al: Amstar 2: A critical appraisal tool for systematic reviews that include randomised or non-randomised studies of healthcare interventions, or both. Bmj 2017; **358:** j4008.
6. Faraday M, Hubbard H, Kosiak B et al: Staying at the cutting edge: A review and analysis of evidence reporting and grading; the recommendations of the american urological association. BJU Int 2009; **104:** 294.
7. Counsil C: Upper tract urothelial cancer (utuc). 2022 Published. Available at: https://www.cancer.org.au/cancer-information/types-of-cancer/rare-cancers/upper-tract-urothelial-cancer
8. Siegel RL, Miller KD, Fuchs HE et al: Cancer statistics, 2022. CA Cancer J Clin 2022; **72:** 7.
9. Wu J, Chen S, Wu X et al: Trends of incidence and prognosis of upper tract urothelial carcinoma. Bosn J Basic Med Sci 2021; **21:** 607.
10. Mohammad NS, Nazli R, Zafar H et al: Effects of lipid based multiple micronutrients supplement on the birth outcome of underweight pre-eclamptic women: A randomized clinical trial. Pak J Med Sci 2022; **38:** 219.
11. Janisch F, Shariat SF, Baltzer P et al: Diagnostic performance of multidetector computed tomographic (mdctu) in upper tract urothelial carcinoma (utuc): A systematic review and meta-analysis. World J Urol 2020; **38:** 1165.
12. Rud E, Galtung KF, Lauritzen PM et al: Examining the upper urinary tract in patients with hematuria-time to revise the ct urography protocol? Eur Radiol 2020; **30:** 1664.
13. David RA, James B, Adeloye D et al: Accuracy of ultrasound vs computed tomography scan for upper urinary tract malignancies and development of a risk-based diagnostic algorithm for haematuria in a uk tertiary centre. Int Urol Nephrol 2021; **53:** 49.
14. Takahashi N, Glockner JF, Hartman RP et al: Gadolinium enhanced magnetic resonance urography for upper urinary tract malignancy. J Urol 2010; **183:** 1330.
15. Cowan NC, Turney BW, Taylor NJ et al: Multidetector computed tomography urography for diagnosing upper urinary tract urothelial tumour. BJU Int 2007; **99:** 1363.
16. Guarnizo E, Pavlovich CP, Seiba M et al: Ureteroscopic biopsy of upper tract urothelial carcinoma: Improved diagnostic accuracy and histopathological considerations using a multi-biopsy approach. J Urol 2000; **163:** 52.
17. Kleinmann N, Healy KA, Hubosky SG et al: Ureteroscopic biopsy of upper tract urothelial carcinoma: Comparison of basket and forceps. J Endourol 2013; **27:** 1450.
18. Vashistha V, Shabsigh A and Zynger DL: Utility and diagnostic accuracy of ureteroscopic biopsy in upper tract urothelial carcinoma. Arch Pathol Lab Med 2013; **137:** 400.
19. Dodd LG, Johnston WW, Robertson CN et al: Endoscopic brush cytology of the upper urinary tract. Evaluation of its efficacy and potential limitations in diagnosis. Acta Cytol 1997; **41:** 377.
20. Low RK, Moran ME and Anderson KR: Ureteroscopic cytologic diagnosis of upper tract lesions. J Endourol 1993; **7:** 311.
21. Sheline M, Amendola MA, Pollack HM et al: Fluoroscopically guided retrograde brush biopsy in the diagnosis of transitional cell carcinoma of the upper urinary tract: Results in 45 patients. AJR Am J Roentgenol 1989; **153:** 313.
22. Potretzke AM, Knight BA, Vetter JM et al: Diagnostic utility of selective upper tract urinary cytology: A systematic review and meta-analysis of the literature. Urology 2016; **96:** 35.
23. Barkan GA, Wojcik EM, Nayar R et al: The paris system for reporting urinary cytology: The quest to develop a standardized terminology. Acta Cytol 2016; **60:** 185.
24. Jin H, Lin T, Hao J et al: A comprehensive comparison of fluorescence in situ hybridization and cytology for the detection of upper urinary tract urothelial carcinoma: A systematic review and meta-analysis. Medicine (Baltimore) 2018; **97:** e13859.

25. van Doeveren T, Nakauma-Gonzalez JA, Mason AS et al: The clonal relation of primary upper urinary tract urothelial carcinoma and paired urothelial carcinoma of the bladder. Int J Cancer 2021; **148:** 981.
26. Lynch HT, Lynch PM, Lanspa SJ et al: Review of the lynch syndrome: History, molecular genetics, screening, differential diagnosis, and medicolegal ramifications. Clin Genet 2009; **76:** 1.
27. Latham A, Srinivasan P, Kemel Y et al: Microsatellite instability is associated with the presence of lynch syndrome pan-cancer. J Clin Oncol 2019; **37:** 286.
28. Lipton LR, Johnson V, Cummings C et al: Refining the amsterdam criteria and bethesda guidelines: Testing algorithms for the prediction of mismatch repair mutation status in the familial cancer clinic. Journal of Clinical Oncology 2004; **22:** 4934.
29. Umar A, Boland CR, Terdiman JP et al: Revised bethesda guidelines for hereditary nonpolyposis colorectal cancer (lynch syndrome) and microsatellite instability. J Natl Cancer Inst 2004; **96:** 261.
30. Vasen HF, Watson P, Mecklin JP et al: New clinical criteria for hereditary nonpolyposis colorectal cancer (hnpcc, lynch syndrome) proposed by the international collaborative group on hnpcc. Gastroenterology 1999; **116:** 1453.
31. Metcalfe MJ, Petros FG, Rao P et al: Universal point of care testing for lynch syndrome in patients with upper tract urothelial carcinoma. J Urol 2018; **199:** 60.
32. Bartley AN, Luthra R, Saraiya DS et al: Identification of cancer patients with lynch syndrome: Clinically significant discordances and problems in tissue-based mismatch repair testing. Cancer Prev Res (Phila) 2012; **5:** 320.
33. Teo MY, Bambury RM, Zabor EC et al: DNA damage response and repair gene alterations are associated with improved survival in patients with platinum-treated advanced urothelial carcinoma. Clin Cancer Res 2017; **23:** 3610.
34. Teo MY, Seier K, Ostrovnaya I et al: Alterations in DNA damage response and repair genes as potential marker of clinical benefit from pd-1/pd-l1 blockade in advanced urothelial cancers. J Clin Oncol 2018; **36:** 1685.
35. Favaretto RL, Shariat SF, Savage C et al: Combining imaging and ureteroscopy variables in a preoperative multivariable model for prediction of muscle-invasive and non-organ confined disease in patients with upper tract urothelial carcinoma. BJU Int 2012; **109:** 77.
36. Messer JC, Terrell JD, Herman MP et al: Multi-institutional validation of the ability of preoperative hydronephrosis to predict advanced pathologic tumor stage in upper-tract urothelial carcinoma. Urol Oncol 2013; **31:** 904.
37. Brien JC, Shariat SF, Herman MP et al: Preoperative hydronephrosis, ureteroscopic biopsy grade and urinary cytology can improve prediction of advanced upper tract urothelial carcinoma. J Urol 2010; **184:** 69.
38. Petros FG, Qiao W, Singla N et al: Preoperative multiplex nomogram for prediction of high-risk nonorgan-confined upper-tract urothelial carcinoma. Urol Oncol 2019; **37:** 292.e1.
39. Ma R, Xia H, Qiu M et al: A diagnostic nomogram of pathologic grade for preoperative risk stratification in upper tract urothelial carcinoma. Clin Med Insights Oncol 2020; **14:** 1179554920927662.
40. Yoshida T, Kobayashi T, Kawaura T et al: Development and external validation of a preoperative nomogram for predicting pathological locally advanced disease of clinically localized upper urinary tract carcinoma. Cancer Med 2020; **9:** 3733.
41. Mori K, Katayama S, Laukhtina E et al: Discordance between clinical and pathological staging and grading in upper tract urothelial carcinoma. Clin Genitourin Cancer 2022; **20:** 95.e1.
42. Subiela JD, Territo A, Mercadé A et al: Diagnostic accuracy of ureteroscopic biopsy in predicting stage and grade at final pathology in upper tract urothelial carcinoma: Systematic review and meta-analysis. Eur J Surg Oncol 2020; **46:** 1989.
43. Malm C, Grahn A, Jaremko G et al: Diagnostic accuracy of upper tract urothelial carcinoma: How samples are collected matters. Scand J Urol 2017; **51:** 137.
44. Su X, Hao H, Li X et al: Fluorescence in situ hybridization status of voided urine predicts invasive and high-grade upper tract urothelial carcinoma. Oncotarget 2017; **8:** 26106.
45. Wang J, Wu J, Peng L et al: Distinguishing urothelial carcinoma in the upper urinary tract from benign diseases with hematuria using fish. Acta Cytol 2012; **56:** 533.
46. Mammen S, Krishna S, Quon M et al: Diagnostic accuracy of qualitative and quantitative computed tomography analysis for diagnosis of pathological grade and stage in upper tract urothelial cell carcinoma. J Comput Assist Tomogr 2018; **42:** 204.
47. Ng CK, Shariat SF, Lucas SM et al: Does the presence of hydronephrosis on preoperative axial ct imaging predict worse outcomes for patients undergoing nephroureterectomy for upper-tract urothelial carcinoma? Urol Oncol 2011; **29:** 27.
48. Scolieri MJ, Paik ML, Brown SL et al: Limitations of computed tomography in the preoperative staging of upper tract urothelial carcinoma. Urology 2000; **56:** 930.

49. Almås B, Øverby S, Halvorsen OJ et al: Preoperative predictors of pathological tumour stage and prognosis may be used when selecting candidates for intensified treatment in upper tract urothelial carcinoma. Scand J Urol 2021; **55:** 100.
50. Yu SH, Hur YH, Hwang EC et al: Does multidetector computed tomographic urography (mdctu) t staging classification correspond with pathologic t staging in upper tract urothelial carcinoma? Int Urol Nephrol 2021; **53:** 69.
51. Goto K, Honda Y, Ikeda K et al: Tumor heterogeneity evaluated by computed tomography detects muscle-invasive upper tract urothelial carcinoma that is associated with inflammatory tumor microenvironment. Sci Rep 2021; **11:** 14251.
52. Yoshida R, Yoshizako T, Maruyama M et al: The value of adding diffusion-weighted images for tumor detection and preoperative staging in renal pelvic carcinoma for the reader's experience. Abdom Radiol (NY) 2017; **42:** 2297.
53. Roy C, Labani A, Alemann G et al: Dwi in the etiologic diagnosis of excretory upper urinary tract lesions: Can it help in differentiating benign from malignant tumors? A retrospective study of 98 patients. AJR Am J Roentgenol 2016; **207:** 106.
54. Milojevic B, Djokic M, Sipetic-Grujicic S et al: Prognostic significance of non-muscle-invasive bladder tumor history in patients with upper urinary tract urothelial carcinoma. Urol Oncol 2013; **31:** 1615.
55. Zeng S, Ying Y, Yu X et al: Impact of previous, simultaneous or intravesical recurrence bladder cancer on prognosis of upper tract urothelial carcinoma after nephroureterectomy: A large population-based study. Transl Androl Urol 2021; **10:** 4365.
56. Venkat S, Khan AI, Lewicki PJ et al: Novel nomograms to predict muscle invasion and lymph node metastasis in upper tract urothelial carcinoma. Urol Oncol 2022; **40:** 108.e11.
57. Kaag M, Trost L, Thompson RH et al: Preoperative predictors of renal function decline after radical nephroureterectomy for upper tract urothelial carcinoma. BJU Int 2014; **114:** 674.
58. Xylinas E, Rink M, Margulis V et al: Impact of renal function on eligibility for chemotherapy and survival in patients who have undergone radical nephro-ureterectomy. BJU Int 2013; **112:** 453.
59. Schwartzmann I, Pastore AL, Saccà A et al: Upper urinary tract urothelial carcinoma tumor seeding along percutaneous nephrostomy track: Case report and review of the literature. Urol Int 2017; **98:** 115.
60. Wu Z, Chen Q, Djaladat H et al: A preoperative nomogram to predict renal function insufficiency for cisplatin-based adjuvant chemotherapy following minimally invasive radical nephroureterectomy (robuust collaborative group). Eur Urol Focus 2022; **8:** 173.
61. Aguilar Palacios D, Wilson B, Ascha M et al: New baseline renal function after radical or partial nephrectomy: A simple and accurate predictive model. J Urol 2021; **205:** 1310.
62. Fajkovic H, Klatte T, Nagele U et al: Results and outcomes after endoscopic treatment of upper urinary tract carcinoma: The austrian experience. World Journal of Urology 2013; **31:** 37.
63. Wen J, Ji ZG and Li HZ: Treatment of upper tract urothelial carcinoma with ureteroscopy and thulium laser: A retrospective single center study. BMC Cancer 2018; **18:** 196.
64. Shenhar C, Veredgorn Y, Bulis S et al: Endoscopic management of low-grade upper tract urothelial carcinoma: Characterizing the long-term burden of care in comparison to radical nephroureterectomy. Urology 2022; **159:** 152.
65. Campi R, Cotte J, Sessa F et al: Robotic radical nephroureterectomy and segmental ureterectomy for upper tract urothelial carcinoma: A multi-institutional experience. World J Urol 2019; **37:** 2303.
66. Kim TH, Lee CU, Kang M et al: Comparison of oncologic and functional outcomes between radical nephroureterectomy and segmental ureterectomy for upper urinary tract urothelial carcinoma. Sci Rep 2021; **11:** 7828.
67. Zhang J, Yang F, Wang M et al: Comparison of radical nephroureterectomy and partial ureterectomy for the treatment of upper tract urothelial carcinoma. Biomed Res Int 2018; **2018:** 2793172.
68. Campbell SC, Clark PE, Chang SS et al: Renal mass and localized renal cancer: Evaluation, management, and follow-up: Aua guideline: Part i. J Urol 2021; **206:** 199.
69. Campbell SC, Uzzo RG, Karam JA et al: Renal mass and localized renal cancer: Evaluation, management, and follow-up: Aua guideline: Part ii. J Urol 2021; **206:** 209.
70. Jeon HG, Jeong IG, Lee JW et al: Prognostic factors for chronic kidney disease after curative surgery in patients with small renal tumors. Urology 2009; **74:** 1064.
71. Hung PH, Tsai HB, Hung KY et al: Increased risk of end-stage renal disease in patients with renal cell carcinoma: A 12-year nationwide follow-up study. Medicine (Baltimore) 2014; **93:** e52.

72. Li L, Lau WL, Rhee CM et al: Risk of chronic kidney disease after cancer nephrectomy. Nat Rev Nephrol 2014; **10:** 135.
73. Malcolm JB, Bagrodia A, Derweesh IH et al: Comparison of rates and risk factors for developing chronic renal insufficiency, proteinuria and metabolic acidosis after radical or partial nephrectomy. BJU Int 2009; **104:** 476.
74. Stiles KP, Moffatt MJ, Agodoa LY et al: Renal cell carcinoma as a cause of end-stage renal disease in the united states: Patient characteristics and survival. Kidney Int 2003; **64:** 247.
75. Jeon HG, Choo SH, Sung HH et al: Small tumour size is associated with new-onset chronic kidney disease after radical nephrectomy in patients with renal cell carcinoma. Eur J Cancer 2014; **50:** 64.
76. Cho A, Lee JE, Kwon GY et al: Post-operative acute kidney injury in patients with renal cell carcinoma is a potent risk factor for new-onset chronic kidney disease after radical nephrectomy. Nephrol Dial Transplant 2011; **26:** 3496.
77. Thadhani R, Pascual M and Bonventre JV: Acute renal failure. N Engl J Med 1996; **334:** 1448.
78. Matin SF, Pierorazio PM, Kleinmann N et al: Durability of response to primary chemoablation of low-grade upper tract urothelial carcinoma using ugn-101, a mitomycin-containing reverse thermal gel: Olympus trial final report. J Urol 2022; **207:** 779.
79. Kleinmann N, Matin SF, Pierorazio PM et al: Primary chemoablation of low-grade upper tract urothelial carcinoma using ugn-101, a mitomycin-containing reverse thermal gel (olympus): An open-label, single-arm, phase 3 trial. Lancet Oncol 2020; **21:** 776.
80. Bin X, Roy OP, Ghiraldi E et al: Impact of tumour location and surgical approach on recurrence-free and cancer-specific survival analysis in patients with ureteric tumours. BJU International 2012; **110:** E514.
81. Chen YT, Yu CC, Yeh HC et al: Endoscopic management versus radical nephroureterectomy for localized upper tract urothelial carcinoma in a high endemic region. Scientific Reports 2021; **11:** 4040.
82. Grasso M, Fishman AI, Cohen J et al: Ureteroscopic and extirpative treatment of upper urinary tract urothelial carcinoma: A 15-year comprehensive review of 160 consecutive patients. BJU International 2012; **110:** 1618.
83. Lee BR, Jabbour ME, Marshall FF et al: 13-year survival comparison of percutaneous and open nephroureterectomy approaches for management of transitional cell carcinoma of renal collecting system: Equivalent outcomes. J Endourol 1999; **13:** 289.
84. Raymundo EM, Lipkin ME, Banez LB et al: Third prize: The role of endoscopic nephron-sparing surgery in the management of upper tract urothelial carcinoma. Journal of Endourology 2011; **25:** 377.
85. Rouprêt M, Hupertan V, Traxer O et al: Comparison of open nephroureterectomy and ureteroscopic and percutaneous management of upper urinary tract transitional cell carcinoma. Urology 2006; **67:** 1181.
86. Seisen T, Nison L, Remzi M et al: Oncologic outcomes of kidney sparing surgery versus radical nephroureterectomy for the elective treatment of clinically organ confined upper tract urothelial carcinoma of the distal ureter. Journal of Urology 2016; **195:** 1354.
87. Hoffman A, Yossepowitch O, Erlich Y et al: Oncologic results of nephron sparing endoscopic approach for upper tract low grade transitional cell carcinoma in comparison to nephroureterectomy - a case control study. BMC Urol 2014; **14:** 97.
88. Upfill-Brown A, Lenis AT, Faiena I et al: Treatment utilization and overall survival in patients receiving radical nephroureterectomy versus endoscopic management for upper tract urothelial carcinoma: Evaluation of updated treatment guidelines. World Journal of Urology 2019; **37:** 1157.
89. Vemana G, Kim EH, Bhayani SB et al: Survival comparison between endoscopic and surgical management for patients with upper tract urothelial cancer: A matched propensity score analysis using surveillance, epidemiology and end results-medicare data. Urology 2016; **95:** 115.
90. Cutress ML, Stewart GD, Zakikhani P et al: Ureteroscopic and percutaneous management of upper tract urothelial carcinoma (utuc): Systematic review. BJU Int 2012; **110:** 614.
91. Cho KS, Hong SJ, Cho NH et al: Grade of hydronephrosis and tumor diameter as preoperative prognostic factors in ureteral transitional cell carcinoma. Urology 2007; **70:** 662.
92. Foerster B, Abufaraj M, Matin SF et al: Pretreatment risk stratification for endoscopic kidney-sparing surgery in upper tract urothelial carcinoma: An international collaborative study. Eur Urol 2021; **80:** 507.
93. Scotland KB, Kleinmann N, Cason D et al: Ureteroscopic management of large ≥2 cm upper tract urothelial carcinoma: A comprehensive 23-year experience. Urology 2018; **121:** 66.
94. Douglawi A, Ghoreifi A, Lee R et al: Bladder recurrence following diagnostic ureteroscopy in patients undergoing nephroureterectomy for upper tract urothelial cancer: Is ureteral access sheath protective? Urology 2022; **160:** 142.
95. Villa L, Cloutier J, Letendre J et al: Early repeated ureteroscopy within 6-8 weeks after a primary endoscopic treatment in patients with upper tract urothelial cell carcinoma: Preliminary findings. World J Urol 2016; **34:** 1201.

96. Oosterlinck W, Kurth KH, Schröder F et al: A prospective european organization for research and treatment of cancer genitourinary group randomized trial comparing transurethral resection followed by a single intravesical instillation of epirubicin or water in single stage ta, t1 papillary carcinoma of the bladder. J Urol 1993; **149:** 749.
97. Sylvester RJ, Oosterlinck W and van der Meijden AP: A single immediate postoperative instillation of chemotherapy decreases the risk of recurrence in patients with stage ta t1 bladder cancer: A meta-analysis of published results of randomized clinical trials. J Urol 2004; **171:** 2186.
98. Gallioli A, Boissier R, Territo A et al: Adjuvant single-dose upper urinary tract instillation of mitomycin c after therapeutic ureteroscopy for upper tract urothelial carcinoma: A single-centre prospective non-randomized trial. J Endourol 2020; **34:** 573.
99. Cutress ML, Stewart GD, Wells-Cole S et al: Long-term endoscopic management of upper tract urothelial carcinoma: 20-year single-centre experience. BJU Int 2012; **110:** 1608.
100. Labbate C, Woldu S, Murray K et al: Efficacy and safety of mitomycin gel (ugn-101) as an adjuvant therapy after complete endoscopic management of upper tract urothelial carcinoma. J Urol 2023**:** 101097ju0000000000003185.
101. Territo A, Fontanet S, Meneghetti I et al: Management of primary upper urinary tract carcinoma in situ diagnosed by ureteroscopic biopsy: Is bacillus calmette-guerin an alternative to nephroureterectomy? Actas Urol Esp (Engl Ed) 2022.
102. Redrow GP, Guo CC, Brausi MA et al: Upper urinary tract carcinoma in situ: Current knowledge, future direction. J Urol 2017; **197:** 287.
103. Metcalf M and Pierorazio PM: Future strategies to enhance kidney preservation in upper urinary tract urothelial carcinoma. Transl Androl Urol 2020; **9:** 1831.
104. Katims AB, Tam AW, Rosen DC et al: Novel treatment of upper tract urothelial carcinoma in situ with docetaxel in bcg refractory patients. Urol Oncol 2021; **39:** 234.e9.
105. Fontanet S, Gallioli A, Baboudjian M et al: Topical instillation of bcg immunotherapy for biopsy-proven primary upper urinary tract carcinoma in situ: A single institution series and systematic review. Urol Oncol 2022.
106. Foerster B, D'Andrea D, Abufaraj M et al: Endocavitary treatment for upper tract urothelial carcinoma: A meta-analysis of the current literature. Urol Oncol 2019; **37:** 430.
107. Giannarini G, Kessler TM, Birkhäuser FD et al: Antegrade perfusion with bacillus calmette-guérin in patients with non-muscle-invasive urothelial carcinoma of the upper urinary tract: Who may benefit? Eur Urol 2011; **60:** 955.
108. Raman JD, Lin YK, Shariat SF et al: Preoperative nomogram to predict the likelihood of complications after radical nephroureterectomy. BJU Int 2017; **119:** 268.
109. Syed JS, Nguyen KA, Suarez-Sariemento A et al: Outcomes of upper tract urothelial cancer managed non-surgically. Canadian Journal of Urology 2019; **26:** 9699.
110. Syed JS, Nguyen KA, Suarez-Sarmiento A et al: Survival outcomes for patients with localised upper tract urothelial carcinoma managed with non-definitive treatment. BJU International 2018; **121:** 124.
111. Chou R, Jungbauer RM and Cheney TP: Management of upper tract urothelial carcinoma: A systematic evidence review, 2022
112. Simone G, Papalia R, Guaglianone S et al: Laparoscopic versus open nephroureterectomy: Perioperative and oncologic outcomes from a randomised prospective study. Eur Urol 2009; **56:** 520.
113. Xylinas E, Rink M, Cha EK et al: Impact of distal ureter management on oncologic outcomes following radical nephroureterectomy for upper tract urothelial carcinoma. Eur Urol 2014; **65:** 210.
114. Abrate A, Sessa F, Sebastianelli A et al: Segmental resection of distal ureter with termino-terminal ureteric anastomosis vs bladder cuff removal and ureteric re-implantation for upper tract urothelial carcinoma: Results of a multicentre study. BJU International 2019; **124:** 116.
115. Capitanio U, Shariat SF, Isbarn H et al: Comparison of oncologic outcomes for open and laparoscopic nephroureterectomy: A multi-institutional analysis of 1249 cases. European Urology 2009; **56:** 1.
116. Ha YS, Chung JW, Choi SH et al: Impact of a bladder cuff excision during radical nephroureterectomy on cancer specific survival in patients with upper tract urothelial cancer in korea: A retrospective, multi-institutional study. Minerva Urologica e Nefrologica 2017; **69:** 466.
117. Jeldres C, Sun M, Isbarn H et al: A population-based assessment of perioperative mortality after nephroureterectomy for upper-tract urothelial carcinoma. Urology 2010; **75:** 315.
118. Kang M, Jeong CW, Kwak C et al: The characteristics of recurrent upper tract urothelial carcinoma after radical nephroureterectomy without bladder cuff excision. Yonsei Medical Journal 2015; **56:** 375.
119. Lughezzani G, Sun M, Perrotte P et al: Should bladder cuff excision remain the standard of care at nephroureterectomy in patients with urothelial carcinoma of the renal pelvis? A population-based study. European Urology 2010; **57:** 956.

120. Nazzani S, Preisser F, Mazzone E et al: Nephroureterectomy with or without bladder cuff excision for localized urothelial carcinoma of the renal pelvis. European Urology Focus 2020; **6:** 298.
121. O'Brien T, Ray E, Singh R et al: Prevention of bladder tumours after nephroureterectomy for primary upper urinary tract urothelial carcinoma: A prospective, multicentre, randomised clinical trial of a single postoperative intravesical dose of mitomycin c (the odmit-c trial). Eur Urol 2011; **60:** 703.
122. Ito A, Shintaku I, Satoh M et al: Prospective randomized phase ii trial of a single early intravesical instillation of pirarubicin (thp) in the prevention of bladder recurrence after nephroureterectomy for upper urinary tract urothelial carcinoma: The thp monotherapy study group trial. J Clin Oncol 2013; **31:** 1422.
123. Freifeld Y, Ghandour R, Singla N et al: Intraoperative prophylactic intravesical chemotherapy to reduce bladder recurrence following radical nephroureterectomy. Urol Oncol 2020; **38:** 737.e11.
124. Yoo SH, Jeong CW, Kwak C et al: Intravesical chemotherapy after radical nephroureterectomy for primary upper tract urothelial carcinoma: A systematic review and network meta-analysis. J Clin Med 2019; **8**.
125. Guo R, Zhu Y, Xiong G et al: Role of lymph node dissection in the management of upper tract urothelial carcinomas: A meta-analysis. BMC Urology 2018; **18:** 24.
126. Chan VW, Wong CHM, Yuan Y et al: Lymph node dissection for upper tract urothelial carcinoma: A systematic review. Arab J Urol 2020; **19:** 37.
127. Zhai TS, Jin L, Zhou Z et al: Effect of lymph node dissection on stage-specific survival in patients with upper urinary tract urothelial carcinoma treated with nephroureterectomy. BMC Cancer 2019; **19:** 1207.
128. Piraino JA, Snow ZA, Edwards DC et al: Nephroureterectomy vs. Segmental ureterectomy of clinically localized, high-grade, urothelial carcinoma of the ureter: Practice patterns and outcomes. Urologic Oncology 2020; **38:** 851.e1.
129. Leow JJ, Chong YL, Chang SL et al: Neoadjuvant and adjuvant chemotherapy for upper tract urothelial carcinoma: A 2020 systematic review and meta-analysis, and future perspectives on systemic therapy. Eur Urol 2021; **79:** 635.
130. Grossman HB, Natale RB, Tangen CM et al: Neoadjuvant chemotherapy plus cystectomy compared with cystectomy alone for locally advanced bladder cancer. N Engl J Med 2003; **349:** 859.
131. Neoadjuvant chemotherapy in invasive bladder cancer: Update of a systematic review and meta-analysis of individual patient data advanced bladder cancer (abc) meta-analysis collaboration. Eur Urol 2005; **48:** 202.
132. Porena M, Mearini E, Mearini L et al: Voiding dysfunction after radical retropubic prostatectomy: More than external urethral sphincter deficiency. Eur Urol 2007; **52:** 38.
133. Margulis V, Puligandla M, Trabulsi EJ et al: Phase ii trial of neoadjuvant systemic chemotherapy followed by extirpative surgery in patients with high grade upper tract urothelial carcinoma. J Urol 2020; **203:** 690.
134. Coleman JA, Yip W, Wong NC et al: Multicenter phase ii clinical trial of gemcitabine and cisplatin as neoadjuvant chemotherapy for patients with high-grade upper tract urothelial carcinoma. J Clin Oncol 2023**:** Jco2200763.
135. Birtle A, Johnson M, Chester J et al: Adjuvant chemotherapy in upper tract urothelial carcinoma (the pout trial): A phase 3, open-label, randomised controlled trial. Lancet 2020; **395:** 1268.
136. Birtle A, Chester J, Jones R et al: Updated outcomes of pout: A phase iii randomized trial of peri-operative chemotherapy versus surveillance in upper tract urothelial cancer (utuc). Journal of Clinical Oncology 2021; **39:** 455.
137. Bellmunt J, Hussain M, Gschwend JE et al: Adjuvant atezolizumab versus observation in muscle-invasive urothelial carcinoma (imvigor010): A multicentre, open-label, randomised, phase 3 trial. Lancet Oncol 2021; **22:** 525.
138. Bajorin DF, Witjes JA, Gschwend JE et al: Adjuvant nivolumab versus placebo in muscle-invasive urothelial carcinoma. N Engl J Med 2021; **384:** 2102.
139. Powles T, Assaf ZJ, Davarpanah N et al: Ctdna guiding adjuvant immunotherapy in urothelial carcinoma. Nature 2021; **595:** 432.
140. Testing mk-3475 (pembrolizumab) after surgery for localized muscle-invasive bladder cancer and locally advanced urothelial cancer (ambassador). Published. Available at: https://clinicaltrials.gov/ct2/show/NCT03244384
141. Zhang X, Wang P, Qi K et al: The role of surgery on primary site in metastatic upper urinary tract urothelial carcinoma and a nomogram for predicting the survival of patients with metastatic upper urinary tract urothelial carcinoma. Cancer Med 2021; **10:** 8079.
142. Nazzani S, Preisser F, Mazzone E et al: Survival effect of nephroureterectomy in metastatic upper urinary tract urothelial carcinoma. Clin Genitourin Cancer 2019; **17:** e602.
143. Chakiryan N, Martinez A, Gao L et al: Optimizing the sequence of chemotherapy for upper tract urothelial carcinoma with clinically positive regional lymph nodes. Journal of Urology 2019; **202:** 76.

144. Khriguian J, Patrocinio H, Andonian S et al: Stereotactic ablative radiation therapy for the treatment of upper urinary tract urothelial carcinoma. Pract Radiat Oncol 2022; **12:** e34.
145. Liu MZ, Gao XS, Qin SB et al: Radiation therapy for nonmetastatic medically inoperable upper-tract urothelial carcinoma. Transl Androl Urol 2021; **10:** 2929.
146. Brown N, Olayos E, Elmer S et al: Renal embolization and urothelial sclerotherapy for recurrent obstructive urosepsis and intractable haematuria from upper tract urothelial carcinoma. Cardiovasc Intervent Radiol 2016; **39:** 467.
147. Kapoor A, Allard CB, Black P et al: Canadian guidelines for postoperative surveillance of upper urinary tract urothelial carcinoma. Can Urol Assoc J 2013; **7:** 306.
148. Seisen T, Granger B, Colin P et al: A systematic review and meta-analysis of clinicopathologic factors linked to intravesical recurrence after radical nephroureterectomy to treat upper tract urothelial carcinoma. Eur Urol 2015; **67:** 1122.
149. Locke JA, Hamidizadeh R, Kassouf W et al: Surveillance guidelines based on recurrence patterns for upper tract urothelial carcinoma. Can Urol Assoc J 2018; **12:** 243.
150. Chang SS, Boorjian SA, Chou R et al: Diagnosis and treatment of non-muscle invasive bladder cancer: Aua/suo guideline. J Urol 2016; **196:** 1021.
151. Katims AB, Say R, Derweesh I et al: Risk factors for intravesical recurrence after minimally invasive nephroureterectomy for upper tract urothelial cancer (robuust collaboration). J Urol 2021; **206:** 568.
152. Li X, Cui M, Gu X et al: Pattern and risk factors of local recurrence after nephroureterectomy for upper tract urothelial carcinoma. World Journal of Surgical Oncology 2020; **18:** 114.
153. Rink M, Xylinas E, Margulis V et al: Impact of smoking on oncologic outcomes of upper tract urothelial carcinoma after radical nephroureterectomy. Eur Urol 2013; **63:** 1082.
154. Lu Y, Zhang W, Fan S et al: Metabolic syndrome and risk of upper tract urothelial carcinoma: A case-control study from surveillance, epidemiology and end results-medicare-linked database. Front Oncol 2020; **10:** 613366.
155. Ehdaie B, Chromecki TF, Lee RK et al: Obesity adversely impacts disease specific outcomes in patients with upper tract urothelial carcinoma. J Urol 2011; **186:** 66.
156. Territo A, Gallioli A, Diana P et al: DNA methylation urine biomarkers test in the diagnosis of upper tract urothelial carcinoma: Results from a single-center prospective clinical trial. J Urol 2022; **208:** 570.
157. Ghoreifi A, Seyedian SL, Piatti P et al: A urine-based DNA methylation marker test to detect upper tract urothelial carcinoma: A prospective cohort study. J Urol 2023**:** 101097ju0000000000003188.
158. Pierconti F, Martini M, Fiorentino V et al: Upper urothelial tract high-grade carcinoma: Comparison of urine cytology and DNA methylation analysis in urinary samples. Hum Pathol 2021; **118:** 42.
159. D'Elia C, Trenti E, Krause P et al: Xpert® bladder cancer detection as a diagnostic tool in upper urinary tract urothelial carcinoma: Preliminary results. Ther Adv Urol 2022; **14:** 17562872221090320.
160. Harsanyi S, Novakova ZV, Bevizova K et al: Biomarkers of bladder cancer: Cell-free DNA, epigenetic modifications and non-coding rnas. Int J Mol Sci 2022; **23**.