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Diagnosis and Management of Non-Metastatic Upper Tract Urothelial Carcinoma: AUA/SUO Guideline

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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).

Materials/Methods: 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. 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 (Table 1).

Results: This Guideline provides updated, evidence-based recommendations regarding diagnosis and management of non-metastatic UTUC including risk stratification, surveillance and survivorship. Treatments discussed include kidney sparing management, surgical management, lymph node dissection (LND), neoadjuvant/adjuvant chemotherapy and immunotherapy.

Conclusion: This standardized guideline seeks to improve clinicians' ability to evaluate and treat patients with UTUC based on available evidence. Future studies will be essential to further support these statements for improving patient care. Updates will occur as the knowledge regarding disease biology, clinical behavior and new therapeutic options develop.

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BACKGROUND

UTUC refers to urothelial tumors that originate from the inner lining of the ureter, calyces, or renal pelvis.[1] Although related in pathogenesis to lower tract (LT) urothelial cancer (bladder and urethra), UTUC is much less common, only affecting 5-10% of all patients with urothelial carcinoma (UC).[2] 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.[3-5]

METHODOLOGY

A full description of the methodology protocol can be found with the unabridged guideline available at www.auanet.org.

GUIDELINE STATEMENTS

Diagnosis and Evaluation

1. For patients with suspected UTUC, a cystoscopy and cross-sectional imaging of the upper tract (UT) 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 LT 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.[6,7] For patients with contraindications to multiphasic CT and magnetic resonance (MR) urography, clinicians may utilize retrograde pyelography in conjunction with non-contrast axial imaging to assess the upper urinary tracts.

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

At ureteroscopic evaluation, clinicians should document key descriptive features of UTUC including tumor size, number, location, focality, and appearance. An example checklist for standardized endoscopic diagnostic examination is provided in Table 2.

There are rare situations where endoscopic UT evaluation may not be necessary, when other diagnostic means clearly confirm the diagnosis of UTUC and thus endoscopic confirmation is not clinically required.

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

The finding of urothelial tumors in the LT (bladder or urethra) warrants appropriate management in the same surgical setting by biopsy, resection or ablation as clinically indicated. The pathology findings from bladder tumor sampling often reflect that of UT tumors, though not reliably enough to be used as rationale for avoiding separate UT endoscopy and biopsy when feasible.[8]

Table 1. *AUA Nomenclature Linking Statement Type to Level of Certainty, Magnitude of Benefit or Risk/Burden, and Body of Evidence Strength*

	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 (No apparent net benefit or harm)	Benefits = Risks/Burdens Best action depends on individual patient circumstances Future research 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 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		

Table 2. *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:	

4. In cases of existing ureteral strictures or difficult access to the UT, 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)

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 can decrease the risk of iatrogenic injury and provide opportunity for a safer procedure.

5. In cases where ureteroscopy cannot be safely performed or is not possible, an attempt at selective UT 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 UT is not possible.[9]

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

Performing UT 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)

LS is common among patients with UTUC, however, LS is frequently unrecognized as a risk factor in this setting and warrants specific attention during clinical assessment.

8. Universal histologic testing of UTUC with additional studies, such as immunohistochemistry or microsatellite instability, 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 3) 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.[10] Routine tissue testing provides a more sensitive, first-line means to identify LS-associated features in tumor samples.

Table 3. *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 2 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 2 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.*[1,2]

Supplemental References
1. 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.
2. 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.

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 inform risk stratification, treatment decision-making and assessment of treatment response.[11,12]

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 4). (Strong Recommendation; Evidence Level: Grade B)

Determining cancer-associated risk is critical to guide risk-adapted treatment selection and patient counseling. The association of high-grade (HG) cancer (HG biopsy or cytology) with disease progression risk and pathologic stage T2 or greater disease defines the category of high-risk (HR) whereas low-grade (LG) cancer (LG biopsy and normal cytology) defines low-risk (LR) disease (Supplementary Appendix I and II, https://www.jurology.com).[13-20]

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

In patients with pre-existing CKD or a solitary kidney, attempts to preserve renal function can be made, if appropriate, with segmental or endoscopic organ-sparing approaches which preferentially are associated with improved postoperative renal function.[21-23]

Treatment

12. Clinicians should provide patients with a description of the short- and long-term risks

Table 4. *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.

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)

Endoscopic management (by retrograde ureteroscopy, antegrade ureteroscopy, or percutaneous resection) is an established treatment option for urothelial cancer, including those involving the UT, and should be the first-line treatment for patients with LR favorable UTUC when technically feasible due to the low rates of metastatic progression.

In certain clinical scenarios of LR UTUC, complete endoscopic ablation may not be feasible. Chemoablation (in-situ tissue destruction) can be a treatment alternative in these situations such as the use of mitomycin containing reverse thermal gel indicated for low grade tumors.[24]

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 radical nephroureterectomy (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. Comparable cancer-specific survival (CSS) and improved renal functional outcomes are reported for carefully selected patients undergoing endoscopic management relative to NU at highly experienced centers (see discussion in the Guideline statement 13).[21,22,25]

15. Tumor ablation may be accomplished via a retrograde or antegrade percutaneous approach and repeat endoscopic evaluation should be performed within 3 months. (Expert Opinion)

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.

16. Following ablation of UTUC tumors and after confirming there is no perforation of the bladder or UT, 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 UC to reduce the rate of intravesical tumor recurrence.[26,27] The principle of an immediate instillation of intravesical or pyelocaliceal (UT) chemotherapy at the time of endoscopic tumor ablation for UTUC as clinical practice is supported by data in this related disease and application.

17. Pelvicalyceal therapy with bacillus Calmette-Guerin (BCG) may be offered to patients with HR favorable UTUC after complete tumor ablation or patients with UT carcinoma in situ. (Expert Opinion)

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

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 with any intervention resulting in dialysis. (Expert Opinion)

Surgical Management

20. Clinicians should recommend RNU or segmental ureterectomy 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 UT 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.

Open, robotic, and laparoscopic approaches are suitable for RNU so long as the above oncologic and surgical principles are followed.

Ureterectomy including SU with ureteroureterostomy and distal ureterectomy with ureteral reimplant are reasonable alternatives to RNU for well-selected patients.[28]

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. Other approaches such as endoscopic assisted tumor ablation are considered alternative options to the gold-standard of extirpative resection and carry risk for UT tumor recurrence, with reported rates of 23% to 76%.[29]

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)

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 segmental ureterectomy (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 randomized control trials (RCTs) have demonstrated that a single instillation of intravesical chemotherapy around the time of NU reduces the risk of subsequent intravesical recurrence of UC.[30,31] 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.[30-32]

There is little data supporting one intravesical chemotherapeutic over another.

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.[33,34]

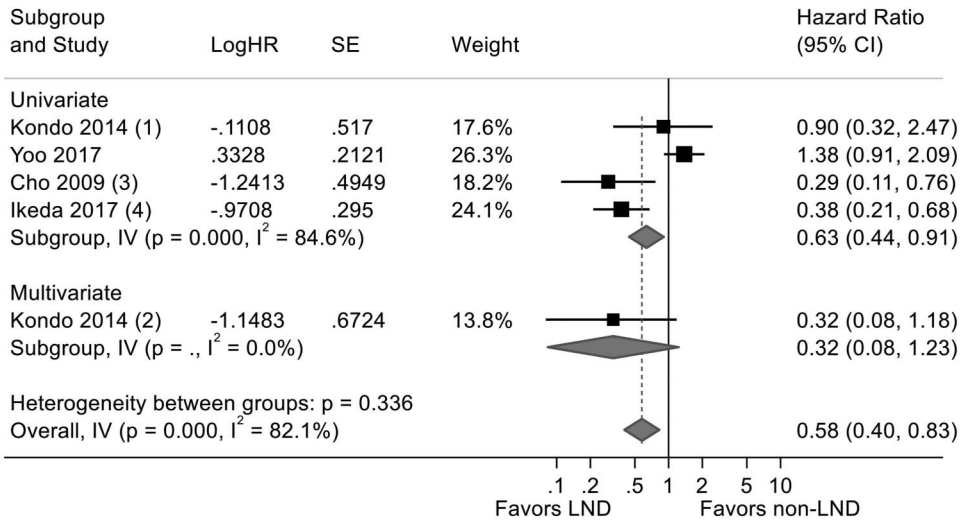
25. For patients with HR UTUC, clinicians should perform LND at the time of NU or ureterectomy. (Strong Recommendation; Evidence Level: Grade B)

In a systematic review by Chan et al., LND was associated with better recurrence-free survival (Figure 1).[34]

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.

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

- **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.

Neoadjuvant/Adjuvant Chemotherapy and Immunotherapy

26. Clinicians should offer cisplatin-based neoadjuvant chemotherapy (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)

Several meta-analyses evaluating NAC for UTUC have identified evidence for improved pathologic outcomes, CSS, and overall survival (OS) with this approach.[35]

Two NAC trials of cisplatin-based chemotherapy prior to RNU strongly support this position.[36,37] Both trials used selection criteria that predicted for existing muscle-invasive disease at baseline in over 65% of patients.[38] In the ECOG 8141 study, 4 cycles of NAC with accelerated MVAC (aMVAC, methotrexate, vinblastine, adriamycin, and cisplatin with growth factor support every 2 weeks) were planned prior to RNU.[39] The pathologic complete response rate (ypT0N0/Nx) following RNU in this group was 13.8% (90% CI: 4.9-28.8). Additionally, 62% of eligible treated patients had final pathologic stage of <ypT1N0/x.

A multicenter prospective Phase II open label trial investigated neoadjuvant split-dose gemcitabine and cisplatin in patients with HG non-metastatic UTUC planned for RNU.[40] This trial met its primary endpoint with 63% of patients achieving <ypT2N0 status following surgery, including 19% with complete pathologic response (ypT0N0).

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.[41] In this study, 261 chemotherapy-naïve patients were identified and enrolled post-RNU, with non-metastatic patients of pT2–T4 pN0–N3 M0 or pTany N1–3. Patients were randomized to platinum chemotherapy based on eligibility (cisplatin, or carboplatin for glomerular filtration rate <50 mL/min) with gemcitabine for 4 planned adjuvant cycles. At a median follow-up of 30.3 months, subjects in the adjuvant chemotherapy arm had improved disease-free survival compared with those on observation.

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 RCTs compared adjuvant checkpoint inhibitor therapy versus observation (IMvigor 010) or placebo (CheckMate 274) following surgery in patients with HR non-metastatic UC (Supplementary Appendix III, https://www.jurology.com).[42,43] 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.

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.

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)

In the case of cN1-3 UTUC, the primary treatment is chemotherapy. Surgery with curative intent may be considered as a consolidation strategy after complete or, in select cases, partial response.

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. LR patients managed with kidney sparing treatment should undergo a follow-up cystoscopy and UT endoscopy within 1-3 months to confirm successful treatment. Once confirmed, these patients should undergo continued cystoscopic surveillance of the bladder at least every 6-9 months

for the first 2 years and then at least annually thereafter. Endoscopy should be repeated at 6 months and 1 year. UT imaging should be performed at least every 6-9 months for 2 years, then annually up to 5 years. Surveillance after 5 years in the absence of recurrence should be based on shared decision making between the patient and clinician. (Expert Opinion)

Endoscopy and radiographic imaging can be utilized to evaluate the UT for recurrence within the affected and contralateral system. 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.

33. HR patients managed with kidney sparing treatment should undergo a follow-up cystoscopy and UT endoscopy with cytology within 1-3 months. Patients with no evidence of disease should undergo cystoscopic surveillance of the bladder and cytology at least every 3-6 months for the first 3 years and then at least annually thereafter. Endoscopy should be repeated at least at 6 months and 1 year. UT imaging should be performed every 3-6 months for 3 years, then annually up to 5 years. surveillance after 5 years in the absence of recurrence should be encouraged and based on shared decision making between the patient and clinician. (Expert Opinion)

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.

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 UT disease. (Expert Opinion)

Patients who develop LT recurrence or a positive cytology without a clear etiology should undergo an evaluation of the UTs.

Surveillance after Radical NU (Summarized in Table 5)

35. After NU, patients with <pT2 N0/M0 disease should undergo surveillance with cystoscopy

Table 5. *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 (eg, 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	0
Upper Tract Endoscopy	-	X	X	-	X	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
Cross-Sectional Imaging*	-	X	X	-	X	-	X	-	X	-	X	-	X	-	-	-	X	-	-	-	X	0
Chest Imaging	-	-	X	-	X	-	X	-	X	-	-	-	X	-	-	-	-	-	-	-	-	-
BMP	-	-	-	-	X	-	-	-	X	-	-	-	X	-	-	-	X	-	-	-	X	-
Post Nephroureterectomy, < pT2, N0/NX																						
Cystoscopy, Cytology	-	X	X	0	X	-	X	-	X	-	-	-	X	-	-	-	X	-	-	-	X	-
Cross-Sectional Imaging*	-	-	X	-	X	-	-	-	X	-	-	-	X	-	-	-	0	-	-	-	0	-
Chest Imaging	-	-	-	-	X	-	-	-	-	-	-	-	-	-	-	-		-	-	-		-
BMP	-	X	-	-	X	-	-	-	X	-	-	-	X	-	-	-	X	-	-	-	X	-
Post Nephroureterectomy, ≥pT2																						
Cystoscopy, Cytology	-	X	X	-	X	-	X	-	X	-	X	-	X	-	-	-	X	-	-	-	X	0
Cross-Sectional Imaging*	-	X	X	-	X	-	X	-	X	-	-	-	X	-	-	-	X	-	-	-	X	0
Chest Imaging	-	X	X	-	X	-	X	-	X	-	-	-	X	-	-	-	X	-	-	-	X	-
BMP	-	X	-	-	X	-	-	-	X	-	-	-	X	-	-	-	X	-	-	-	X	-

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

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

and cytology within 3 months after surgery, then repeated based on pathologic grade. For LG this should repeated at least every 6-9 months for the first 2 years and then at least annually thereafter. For HG, this should be repeated at least every 3-6 months for the first 3 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 5 years in the absence of recurrence should be encouraged and based on shared decision making between the patient and clinician (See Table 5). (Expert Opinion)

Bladder recurrence after NU for patients with non-muscle invasive, node-negative UTUC is common and warrants specific follow up for early detection with a schedule of routine surveillance cystoscopy during the first 2 years.[44,45] After 2 years, the frequency can be significantly reduced in patients without recurrences though, as with non-muscle invasive bladder cancer, the duration of surveillance long-term is not clear.[46] Bladder recurrences should be managed according to established guidelines. Periodic imaging of the UTs should be undertaken given the risk of recurrence to the contralateral UT, preferably with cross-sectional imaging such as CT urogram, though the rate is low enough that this can be done annually after NU.

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 3 months after surgery, then every 3-6 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 3-6 months for years 1 and 2, every 6 months at year 3, and annually thereafter to year 5. A clinician should perform chest imaging, preferably with chest CT, every 6-12 months for the first 5 years. Beyond 5 years after surgery in patients without recurrence, ongoing surveillance with cystoscopy and UT imaging may be continued on an annual basis according to principles of shared/informed decision-making. (Expert Opinion)

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.[44] Risk adapted surveillance with cystoscopy and urine cytology at routine intervals is indicated to facilitate early detection of bladder recurrences.

The additional high risk of locoregional recurrence and metastasis in patients with ≥ pT2 UTUC warrants risk-adapted routine surveillance with contrast-enhanced cross-sectional imaging and urography, with decreasing intensity in years 3 to 5, and subsequent follow-up surveillance recommended according to principles of shared decision-making.

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)

Risk factors such as smoking are associated with advanced disease stage, recurrence and worse cancer-specific mortality among patients with UTUC, with the highest risk among current smokers.[47] UTUC is also associated with metabolic syndrome and obesity, with obesity adversely impacting disease-specific outcomes among patients undergoing RNU.[48,49] 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

Recent studies have identified significant genomic distinctions between primary UTUC and primary bladder cancers, namely a higher prevalence of activating mutations (fibroblast growth factor receptor 3) in UTUC. Genomic markers may also prove useful as less non-invasive biomarkers of tumor grade and stage and for identifying potential pathways for directed treatment.[50] Improvements in flexible digital endoscopes have greatly improved visualization and access to the upper urinary tract. Instrumentation to allow for effective and safe tissue sampling has been much slower to develop. Newer devices are in development that may leverage the ability of robotic endoscopy to offer better and more precise endoscopic surgical capabilities.

DISCLAIMER

This document was written by the Upper Tract Urothelial Carcinoma Guideline 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 committee chairs. Panel members were selected by the chairs. Membership of the Panel included specialists in urology and medical oncology 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 treatment of non-metastatic UTUC. Funding of the panel was provided by the AUA. Panel members received no remuneration for their work. Each member of the panel provides an ongoing conflict of interest disclosure to the AUA, and the Panel Chair, with the support of AUA Guidelines staff and the PGC, reviews all disclosures and addresses any potential conflicts per AUA's Principles, Policies and Procedures for Managing Conflicts of Interest. 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 which are too new to be addressed by this guideline as necessarily experimental or investigational.

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