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Review Article

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Contemporary Management of Upper Tract Urothelial Carcinoma: Transitioning Toward Organ Preservation and Precision Oncology

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Abstract

The management of upper tract urothelial carcinoma (UTUC), which represents 5–10% of urothelial tumours and has traditionally been treated with radical nephroureterectomy with bladder cuff excision (RNU), has undergone significant transformation over the past two decades due to concerns regarding morbidity and renal functional decline. This review evaluates evolving understanding of risk factors distinguishing UTUC from bladder cancer, advances in diagnostic evaluation, the development of risk-stratification models, and the emergence of kidney-sparing strategies, chemoablation, and precision oncology. Recent literature highlights improvements in CT urography, high-definition and image-enhanced ureteroscopy, refined biopsy tools, and molecular diagnostics, all of which have enhanced diagnostic accuracy and enabled more precise risk stratification. These innovations support safe use of kidney-sparing surgery, including endoscopic ablation and segmental ureterectomy in low-risk UTUC, achieving oncologic outcomes comparable to RNU while preserving renal function, while topical chemoablation agents such as mitomycin gel (UGN-101) further expand renal-preserving options. For high-risk or metastatic disease, perioperative systemic chemotherapy, immune checkpoint inhibitors, and antibody drug conjugates now play an increasing role, though lifelong surveillance remains essential due to high recurrence rates in the bladder and contralateral tract. Overall, UTUC management has shifted from a uniform radical approach toward a precision-based, risk-adapted paradigm that balances oncologic control with renal preservation, with future directions focused on refining molecular biomarkers, validating kidney-sparing approaches in higher-risk cohorts, and expanding targeted systemic therapies.

Introduction:

Upper tract urothelial carcinoma (UTUC) represents a relatively uncommon malignancy, accounting for approximately 5–10% of all urothelial tumors[1]. Radical nephroureterectomy (RNU) with bladder cuff excision has traditionally been regarded as the gold standard for management; however, this procedure is associated with significant morbidity and may lead to a decline in renal function[1]. In recent years, the approach to managing UTUC has changed considerably. This shift is due to better understanding of the disease's risk factors, insights into how its genetics differ from bladder cancer, enhanced diagnostic methods, more accurate ways to categorize risk, increased use of minimally invasive procedures, and the introduction of new systemic treatments[2]. Enhanced imaging modalities improved endoscopic technologies, and deeper insights into tumor biology have enabled

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tailored, risk-adapted treatment strategies that optimize oncologic outcomes while preserving renal function[3,4]. Furthermore, the integration of perioperative systemic therapy, including immunotherapy and targeted agents, has expanded the therapeutic landscape beyond traditional surgical approaches[5,6]. This evolving paradigm is built on three central pillars. First one is the risk stratification to guide treatment intensity and individualize management, second is adoption of kidney-sparing surgery (KSS) as the preferred approach for appropriately selected low-risk cases[3,4] and emerging third pillar is integration of genomic profiling and novel systemic therapies, particularly immune checkpoint inhibitors, for advanced disease[2,6]. These advances represent a move toward tailored, multidisciplinary, and precision care, aiming to enhance survival and quality of life for UTUC patients. This review outlines the evolution of this paradigm shift and summarizes the supporting evidence, and discusses future directions in the management of UTUC.

Risk Factors:

Bladder cancer (BC) and upper tract urothelial carcinoma (UTUC) share some causes but differ in certain risk patterns. Cigarette smoking is the primary risk factor for both, responsible for about 50% of BC cases and raising UTUC risk two to three times in smokers compared to non-smokers[7]. Occupational exposure to aromatic amines, historically prevalent in industries such as dye, rubber, and textile manufacturing, is a well-established risk for both BC and UTUC, though its contribution is generally more pronounced in bladder cancer. Some risk factors are unique to UTUC; for example, chronic use of analgesics containing phenacetin is closely tied to UTUC but rarely linked to bladder cancer[8]. Aristolochic acid, found in some herbal remedies and contaminated grains, is a significant environmental carcinogen in areas like the Balkans and East Asia, and is strongly linked to UTUC development. In addition, hereditary nonpolyposis colorectal cancer (HNPCC), also known as Lynch syndrome—particularly cases involving MSH2 gene mutations—markedly elevates the risk of upper tract urothelial carcinoma (UTUC), with a lifetime risk reaching up to 20%. This contrasts with its relatively minor effect on bladder cancer risk.[1]p In contrast, bladder cancer is more commonly associated with schistosomiasis, especially in endemic regions, leading to squamous cell changes, whereas this is rarely linked to UTUC[11]. Chronic irritation, infections, or stones can contribute to both cancers, but are more strongly implicated in the pathogenesis of UTUC when involving long-standing inflammation of the upper tract. Furthermore, having a history of bladder cancer raises the likelihood of developing subsequent UTUC, and the reverse is also true. This pattern reflects the concept of "field cancerization" within the urothelium[1].

Diagnostic Evaluation: Accurate and timely diagnosis is a cornerstone of effective management of upper tract urothelial carcinoma (UTUC). Historically, diagnosis relied heavily on **intravenous urography (IVU)** and **retrograde pyelography**, supplemented by **urine cytology**. Although these techniques continue to be beneficial, they have been predominantly replaced by multiphase computed tomography urography (CTU), which is now considered the gold standard imaging modality for assessing the upper urinary tract. CTU demonstrates high sensitivity (88–100%) and specificity (93–99%) for UTUC, facilitating comprehensive visualization of the urothelial lining as well as adjacent anatomical structures (see Table 1)[1,12-16].

Table 1 : *Imaging Modalities in the Diagnosis of Upper Tract Urothelial Carcinoma (UTUC)*

Imaging Modality	Sensitivity (%)	Specificity (%)	Key Diagnostic Features / Remarks
CT Urography (CTU)	92–97	93–99	Gold standard imaging for UTUC; detects filling defects, wall thickening, and hydronephrosis.
Magnetic Resonance Urography (MRU)	75–85	80–90	Used when CT is contraindicated; good soft-tissue contrast but lower resolution.
Ultrasound (USG)	45–60	80–85	Detects hydronephrosis or large masses; poor for small or flat lesions.
Intravenous Urography (IVU)	50–75	80–85	Obsolete; limited sensitivity but useful for gross filling defects.
Retrograde Pyelo graphy (RPG)	85–90	85–90	Direct visualization; useful when CT findings are equivocal.
PET/CT	70–85	80–90	Useful in staging and detecting metastases; not first-line diagnostic tool.
Ureteroscopic Evaluation with Biopsy	90–95	98	Provides direct visualization and histological confirmation.

Diagnostic ureteroscopy (URS) with targeted biopsy represents another major advancement. URS permits direct visualization of lesions, acquisition of histologic specimens, and assessment of tumor characteristics such as size, multifocality, and architecture, which are essential for accurate **risk stratification**[3,17]. Biopsy of upper tract lesions plays a crucial role in confirming diagnosis, grading the tumor, and informing risk stratification to guide management. Historically, obtaining adequate tissue from the upper urinary tract was technically challenging due to limited access, small-caliber instruments, and poor visualization. Over the past two decades, several technological and procedural advances have significantly improved the accuracy, safety, and diagnostic yield of upper tract biopsies. Introduction of flexible digital ureteroscope offer enhanced maneuverability, superior image resolution, and better irrigation control compared to older fiberoptic models. This has enabled improved target visualization, precise biopsy of small or difficult-to-reach lesions, and lower risk of missing flat or subtle tumors. High-definition imaging also facilitates more accurate determination of tumor characteristics (e.g., papillary vs sessile), which is essential for risk stratification. Diagnostic sensitivity of ureteroscopic biopsy has increased to 85–90% for high-grade tumors with these devices[1,5,18,19]. Development of smaller but more effective biopsy forceps (e.g., BIGopsy®, Piranha®) has allowed retrieval of larger, higher-quality tissue samples without increasing complication rates. Compared with earlier "cold cup" forceps, these modern instruments produce specimens with better preserved histologic architecture, enabling more reliable tumor grading. Some series report diagnostic rates of up to 95% for tumor grading using these enhanced forceps[20,21]. The use of ureteral access sheaths and wire-guided biopsy techniques has improved stability during ureteroscopy, reducing mucosal trauma and facilitating repeated, targeted sampling when needed. This allows for safer biopsies in the proximal ureter and renal pelvis, which have traditionally been difficult areas to access[3]. Narrow-band imaging (NBI) and image-enhanced endoscopy improve detection of flat carcinoma in situ (CIS) and subtle lesions that may not be evident under white light[19]. Confocal laser endomicroscopy (CLE) allows real-time in vivo microscopic assessment, improving diagnostic precision and potentially reducing the number of biopsies required[22]. Improved tissue handling and fixation protocols, along with immunohistochemistry and molecular profiling, have enhanced the interpretability and prognostic value of small biopsy samples[23,24].

Urine cytology serves as a supplementary diagnostic method for upper tract urothelial carcinoma (UTUC), particularly in the identification of high-grade lesions. Although its sensitivity is limited for low-grade tumors, urine cytology can detect malignant urothelial cells originating from the renal pelvis or ureter. The technique is especially effective when selective upper tract sampling is performed via ureteral catheterization, offering improved diagnostic accuracy over voided specimens[1].

Molecular Diagnostic Tests in Upper Tract Urothelial Carcinoma

Molecular diagnostics have emerged as important adjuncts to imaging, cytology, and ureteroscopic biopsy in the evaluation of upper tract urothelial carcinoma (UTUC), particularly when considering kidney-sparing management. Urine cytology remains a widely used non-invasive tool with high specificity but limited sensitivity, especially in low-grade disease. FGFR3 mutations are enriched in low-grade UTUC and can support tumour characterization and potential response to FGFR-targeted therapy[25]. Fluorescence in situ hybridization (UroVysion® FISH), detecting aneuploidy of chromosomes 3, 7, 17 and deletion of 9p21, demonstrates superior detection of high-grade UTUC and carcinoma in situ, with reported sensitivities of 65–80% and specificities of 80–90%[26]. Tumour-specific DNA alterations are increasingly measurable in urine, most notably TERT promoter mutations, which show high specificity and association with recurrence risk[27]. DNA methylation-based assays, incorporating hypermethylated gene panels, have shown sensitivities of 80–90% and may outperform cytology in early-stage disease[28]. Emerging platforms include urinary microRNA-based signatures, circulating tumour DNA, and next-generation sequencing (NGS) from urine or tissue, enabling molecular subtyping and therapeutic stratification[29]. Despite increasing clinical promise, cost, assay variability, and limited availability currently restrict widespread use, and molecular markers remain complementary rather than standalone diagnostic tests.

Collectively, these advances in urine imaging, endoscopic evaluation, and molecular diagnostics have

transformed UTUC diagnosis from a largely radiographic exercise to a multimodal, precision-based process, enabling tailored therapeutic decision-making and more accurate prognostication

Risk Stratification

The primary goal of risk stratification is to differentiate between low-risk and high-risk disease. This is based on a combination of clinical, radiological, endoscopic (biopsy), and laboratory findings. Low-risk UTUC tumors have a high likelihood of being non-invasive and are amenable to kidney-sparing treatments. Typical characteristics includes, unifocal tumor, small tumor size (< 2 cm), low-grade cytology (or absence of high-grade), low-grade on biopsy (if obtainable), non invasive appearance on CT urogram (e.g., no hydronephrosis, no obvious muscle-invasive mass)[1]. Solitary kidney, renal insufficiency, or significant comorbidities (this influences the decision towards kidney-sparing even if other features are ambiguous). High-risk UTUC tumors have a significant potential for invasion, metastasis, and recurrence. They typically require radical nephroureterectomy (RNU). Typical characteristics include multifocal tumor, large tumor size (≥2 cm), high-grade cytology, high-grade on biopsy, radiographic evidence of invasion (e.g., hydronephrosis, a large infiltrative mass on CT), variant histology (e.g., micropapillary, sarcomatoid, plasmacytoid), concurrent CIS (carcinoma in situ), previous radical cystectomy for bladder cancer (Table- II)

Kidney-Sparing Surgery

Kidney-sparing surgery (KSS) has emerged as a valuable management approach for carefully selected patients with upper tract urothelial carcinoma (UTUC), aiming to preserve renal function without compromising oncological outcomes. Radical nephroureterectomy (RNU) has long been considered the standard treatment, but for low-risk UTUC, kidney-sparing surgery (KSS) offers similar cancer control while reducing complications and better preserving kidney function. Both endoscopic ablation and segmental ureterectomy have shown favorable results when combined with strict surveillance and appropriate patient selection. Seisen et al. found no statistically significant difference in cancer-specific survival between kidney-sparing surgery (KSS) and radical nephroureterectomy (RNU), providing additional evidence that kidney preservation is a safe alternative for appropriately selected patients[3]. Careful selection of patients, tumour risk assessment, and thorough follow-up are crucial because conservative management carries a higher risk of local recurrence. Current prospective studies and registry data are continually updating the guidelines, methods, and long-term results for KSS to achieve optimal kidney preservation without compromising cancer safety[1,]t .

Segmental Ureteric Resection

Segmental ureteric resection (SUR) is an established kidney-sparing surgical option for the management of low-grade, non-invasive urothelial carcinoma localized

Table II. Risk stratification in upper tract urothelial carcinoma (adapted from AUA guidelines).

	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 TractInvolvement**	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

to the ureter, particularly in the mid- or distal ureter. This procedure allows complete oncologic excision of the affected ureteral segment with subsequent ureteroureterostomy or ureteroneocystostomy, depending on the tumor's location[1]. In carefully selected patients with unifocal, low-grade tumors, SUR offers oncological outcomes comparable to radical nephroureterectomy (RNU) while providing the benefit of renal function preservation[30]. The European Association of Urology (EAU) guidelines recommend SUR as a definitive treatment in cases where complete resection with negative margins is achievable and in patients with imperative indications such as a solitary kidney or renal insufficiency[1]. Advances in laparoscopic and robotic-assisted techniques have further improved the precision and postoperative recovery of this approach. Although local recurrence can occur in the remaining urothelium, meticulous patient selection, intraoperative frozen section margin assessment, and postoperative surveillance are critical to maintaining favorable outcomes[1]. Thus, SUR represents a safe and effective kidney-sparing strategy for appropriately selected cases of low-grade ureteric urothelial carcinoma.

Percutaneous and Retrograde Tumor Ablation

Percutaneous and retrograde tumor ablation techniques represent essential components of kidney-sparing management for selected patients with upper tract urothelial carcinoma (UTUC), particularly those with low-grade, non-invasive, and unifocal disease. The retrograde (ureteroscopic) approach allows direct visualization and endoscopic resection or ablation using holmium: YAG or thulium lasers, facilitating precise tumor destruction with minimal morbidity[31,32]. In contrast, the percutaneous approach—performed through a nephrostomy tract—offers superior access to large, complex, or inaccessible renal pelvic tumors, enabling complete resection or laser ablation under nephroscopic guidance[22]. Both modalities aim to preserve renal parenchyma and function while maintaining oncological safety. Comparative studies have demonstrated similar cancer-specific survival rates between endoscopic ablation and radical nephroureterectomy in carefully selected low-risk cases[32,33]. However, the risk of tumor recurrence and potential tumor seeding along the percutaneous tract remain key concerns, underscoring the need for meticulous case selection. However, post ablation adjuvant instillation therapy(e.g., mitomycin C), and rigorous postoperative surveillance can reduce the chance of recurrence[22,31]. When performed in specialized centers with experienced surgeons, percutaneous and retrograde ablation offer effective, minimally invasive kidney-sparing alternatives in the management of UTUC[33]. Tumor seeding risk with percutaneous approach is now <1% with modern technique.

Chemoablation

Chemoablation has emerged as an innovative component of the kidney-sparing approach for managing upper tract urothelial carcinoma (UTUC), particularly in patients with low-grade, non-invasive disease who are unsuitable for or wish to avoid radical nephroureterectomy. This technique involves the instillation of topical chemotherapeutic agents directly into the upper urinary tract to achieve local tumor eradication while preserving renal function. Recent advances, such as the development of mitomycin gel (UGN-101; Jelmyto), have significantly improved drug dwell time and local efficacy compared with earlier liquid instillations[1,34]. The OLYMPUS trial, a pivotal phase III study, demonstrated that chemoablation with UGN-101 achieved a complete response rate of 58% in patients with low-grade UTUC after six instillations, with durable responses observed in follow-up[34]. While the procedure offers a minimally invasive, nephron-sparing alternative, potential complications such as ureteric stenosis and local irritation remain important considerations. Ongoing research aims to refine delivery systems, optimize dosing regimens, and evaluate combination strategies to enhance the efficacy and safety of chemoablation in the conservative management of UTUC.

Partial Nephrectomy for Upper Tract Urothelial Carcinoma

Partial nephrectomy is an uncommon but valuable kidney-sparing surgical option for select cases of upper tract urothelial carcinoma (UTUC), particularly when the tumor is localized to the renal pelvis or calyceal system and amenable to complete resection with negative margins. Although radical nephro-ureterectomy (RNU) remains the gold standard for most cases, partial nephrectomy may be considered in imperative situations—such as solitary kidney, bilateral disease, or pre-existing renal insufficiency—where renal preservation is critical[1,35]. Advances in surgical techniques, including laparoscopic and robotic-assisted approaches, have enhanced the feasibility and safety of this procedure, offering

reduced morbidity and improved postoperative recovery[36]. Oncologic outcomes from small retrospective series suggest that, in highly selected low-grade, non-invasive tumors, partial nephrectomy can achieve comparable cancer-specific survival to RNU while maintaining superior renal function[35,36]. However, recurrence within the residual collecting system remains a significant concern, necessitating close endoscopic and radiologic surveillance postoperatively[1]. Due to limited evidence and small sample sizes, partial nephrectomy is currently reserved for exceptional indications, pending further validation from multicenter prospective studies[36].

Treatment Options for High-Risk Upper Tract Urothelial Carcinoma

High-risk upper tract urothelial carcinoma (UTUC) is characterized by high-grade histology, large tumor size (>2 cm), multifocality, hydronephrosis, or evidence of invasion on imaging. The gold standard treatment for high-risk disease remains radical nephroureterectomy (RNU) with excision of a bladder cuff, which offers optimal oncologic control[1]. The procedure can be performed via an open, laparoscopic, or robot-assisted approach without compromising oncologic outcomes[37]. In recent years, perioperative systemic chemotherapy has been integrated into treatment paradigms to improve survival outcomes. Neoadjuvant platinum-based chemotherapy is preferred due to better renal function pre-RNU, allowing optimal dosing and demonstrating a survival benefit in multiple studies[38,39]. Adjuvant chemotherapy is indicated in patients with pT2–T4 or node-positive disease when neoadjuvant therapy has not been given[5]. **In cases with locally advanced or metastatic disease, s**ystemic therapy with immune checkpoint inhibitors (ICIs) such as pembrolizumab or nivolumab is recommended, particularly in platinum-ineligible or refractory cases[40,41]. Adjuvant nivolumab following RNU in high-risk patients has shown improved disease-free survival compared to placebo[42]. Bladder recurrence prophylaxis with a single postoperative instillation of intravesical chemotherapy (e.g., mitomycin C) reduces subsequent bladder tumor formation[43]. For patients unfit for RNU, segmental ureterectomy or endoscopic ablation may be considered in selected cases with imperative indications, though these carry a higher risk of recurrence[44]. Ongoing research into genomic profiling and precision oncology may further refine therapy selection and improve individualized treatment outcomes in high-risk UTUC[45].

Precision Oncology in Upper Tract Urothelial Carcinoma (UTUC)

Precision oncology has revolutionized the management of upper tract urothelial carcinoma (UTUC) by focusing on individualized treatment strategies guided by molecular and genomic profiling rather than uniform therapeutic approaches. Recent advances in next-generation sequencing (NGS) have shown that UTUC possesses unique genetic alterations distinct from bladder urothelial carcinoma, with FGFR3, HRAS, and KMT2D mutations commonly seen in low-grade tumors, while TP53 and RB1 mutations are more prevalent in high-grade disease[45,46]. Identification of these molecular subtypes has enabled the application of targeted therapies, such as FGFR inhibitors (e.g., erdafitinib) for FGFR3-mutated tumors[47], and immune checkpoint inhibitors (e.g., pembrolizumab, nivolumab) based on PD-L1 expression and tumor mutational burden[48]. The development of circulating tumor DNA (ctDNA) and urinary biomarkers creates new possibilities for early diagnosis, tracking minimal residual disease, and making timely changes in treatment plans. With the ongoing integration of genomic information into clinical procedures, precision oncology is set to transform how UTUC patients are assessed and treated. This approach aims to tailor therapies more effectively, reducing unnecessary treatments and enhancing patient outcomes.

Follow-Up and Surveillance

Monitoring and regular check-ups play a crucial role in caring for patients who have received treatment for upper tract urothelial carcinoma (UTUC). These approaches help identify local recurrence, metastasis, or the development of new bladder tumors while they are still at an early, manageable phase. The intensity and frequency of surveillance depend on tumor risk category, pathological stage, and type of surgical intervention. After radical nephroureterectomy (RNU), cystoscopy and urinary cytology are recommended every 3–6 months during the first two years and annually thereafter, given that bladder recurrence occurs in up to 30–50% of patients[1,49]. Cross-sectional imaging of the abdomen and pelvis using CT urography or MRI should be performed every 6–12 months for the first 2–3 years to detect local or distant recurrence[50]. In patients undergoing kidney-sparing

surgery (KSS), a more intensive surveillance schedule is required, including ureteroscopic evaluation, cytology, and imaging every 3–6 months during the first two years, followed by annual follow-up[51]. Urinary cytology remains the cornerstone for detecting recurrence, while novel urinary biomarkers and circulating tumor DNA (ctDNA) show promise as non-invasive tools for future personalized surveillance protocols[52]. Adherence to risk-adapted follow-up schedules ensures early detection of recurrence, preserves renal function, and improves overall oncological outcomes.

Conclusion

The management of upper tract urothelial carcinoma (UTUC) has evolved significantly from a one-size-fits-all radical surgical approach to a precision-based, risk-adapted strategy that balances oncological safety with renal preservation. Advances in diagnostic evaluation, risk stratification, and kidney-sparing surgical techniques have enabled more tailored and effective treatments for patients with low-risk UTUC. Chemoablation and the integration of systemic therapies, including immunotherapy and targeted agents, have further expanded the therapeutic landscape, offering new options for patients with high-risk or metastatic disease. Lifelong surveillance remains critical due to the high recurrence risk in the bladder and contralateral tract. Future directions include further refinement of molecular biomarkers, validation of kidney-sparing surgery in higher-risk cohorts and expanded use of targeted systemic therapies

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