The biologic landscape and therapeutic implications of upper tract urothelial cancer

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Purpose of review
Management of upper tract urothelial cancer (UTUC) has been largely extrapolated from bladder cancer due to its rarity; however, unique biological and clinical differences between UTUC and bladder cancer have been uncovered. The purpose of this review is to present the current therapeutic landscape of UTUC with an emphasis on biologically driven rationale.

Recent findings
Prospective trials for patients with high-risk localized UTUC have shown improved outcomes with adjuvant and neoadjuvant platinum-based chemotherapy. However, the timing of therapy relative to nephroureterectomy may impact platinum eligibility due to renal functional decline following surgery. In recent years, emerging therapeutic classes including immune checkpoint inhibition, antibody drug conjugates, and targeted therapies have emerged as tolerable alternatives to platinum-based chemotherapy in treating metastatic disease. Biomarker-selected therapies, including those targeting HER2 and FGFR3, have shown encouraging results and are relevant to UTUC based on increased expressions of these targets; however, no prospective study to date has been powered to assess the effect of these modern treatments on patients with UTUC specifically.

Summary
Unique biological insights into UTUC pathogenesis and risk factors have expanded the therapeutic landscape for these patients beyond conventional platinum-based chemotherapeutic approaches. Novel therapeutic classes have emerged to guide more precise approaches in treating patients with urothelial cancer, with a need for further trials powered specifically to the UTUC population.

Keywords
antibody–drug conjugates, immune checkpoint inhibition, perioperative therapy, targeted therapy, upper tract urothelial cancer

INTRODUCTION

Upper tract urothelial cancer (UTUC) is a rare type of urothelial cancer (UC) located in the ureters and renal pelvis, accounting for <5–10% of all UC [1,2]. Due to similarities between UTUC and UC of the bladder, approaches to managing UTUC have been largely extrapolated from evidence in bladder UC, and systemic therapy has traditionally involved cisplatin-based chemotherapy regimens. However, an improved understanding of UTUC pathogenesis and risk factors has expanded therapeutic options for these patients.

Similar to bladder UC, tobacco exposure remains one of the main risk factors for UTUC [1,3]. However, other risk factors have been uniquely associated with UTUC. For example, compared to bladder UC, hereditary forms of UTUC have been associated with microsatellite instability, alterations in mismatch repair (MMR) genes, and Lynch syndrome [4–6].

Mutational profile differences have also been identified between bladder UC and UTUC, suggesting biological differences between these entities. A recent study reported somatic mutations in *FGFR3* (35.6% vs. 21.6%), *HRAS* (13.6% vs. 1.0%), and *CDKN2B;* (15.3% vs. 3.9%) to be more common in

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KEY POINTS

- The management of upper tract urothelial cancer (UTUC) has been largely extrapolated from bladder cancer, but unique differences in biology and risk factors exist between these entities.
- Phase 2 and 3 trials designed specifically for patients with UTUC have demonstrated improved outcomes with adjuvant and neoadjuvant platinum-based chemotherapy in high-risk localized disease.
- Neoadjuvant therapy for high-risk localized disease is often favored due to surgery-related renal function decline that can limit patients' eligibility for platinum chemotherapy adjuvantly.
- The combination of enfortumab vedotin and pembrolizumab is the newest first-line treatment for advanced urothelial cancer, including UTUC, while later line options continue to expand, including sacituzimab govitecan, trastuzumab deruxtecan, and erdafitinib.
- The identification of specific biomarkers to precisely inform treatment decisions and trials powered to evaluate the efficacy of these agents specifically in UTUC remain unmet needs.

UTUC tumors, while *TP53* (25.4% vs. 57.8%), *RB1* (0.0% vs. 18.6%), and *ARID1A* (13.6% vs. 27.5%) were more commonly mutated in bladder tumors [4–7].

Here, we review the contemporary therapeutic landscape of UTUC with an emphasis on biologically driven rationale.

PERIOPERATIVE SYSTEMIC THERAPY FOR NONMETASTATIC UPPER TRACT UROTHELIAL CANCER

Platinum-based chemotherapy is FDA-approved for eligible patients with UC in the neoadjuvant and adjuvant setting and remains a first-line option for patients with metastatic disease [8,9]. However, limited prospective data exist specifically for patients with UTUC (Table 1).

Neoadjuvant chemotherapy

The gold standard treatment for high-risk, clinically nonmetastatic high grade UTUC is radical nephroureterectomy (RNU). In the peri-operative setting neoadjuvant platinum-based chemotherapy is often favored, as postoperative changes in renal function may affect platinum eligibility [10,11]. Furthermore, treatment in the neoadjuvant setting provides information regarding tumor chemosensitivity. Several retrospective studies have shown neoadjuvant chemotherapy improves progression free (PFS) and overall (OS) survival with an association of pathologic downstaging and complete response with survival outcomes [12–17].

ECOG-ACRIN 8141, a single-arm, phase 2 clinical trial evaluated pathologic response of neoadjuvant chemotherapy (NAC) for high grade UTUC [18]. Thirty-six patients were assigned to treatment with accelerated methotrexate, vinblastine, doxorubicin, and cisplatin (aMVAC) based on eGFR >50 ml/min. Of the 29 patients eligible for aMVAC, 4 (13.8%) achieved ypT0N0/ypT0Nx [90% confidence interval (CI) 4.9–28.8], and 18 (62%) had a post nephroureterectomy pathological stage of ypT1 or less. Two patients had recurrent bladder cancer. With respect to toxicity, 7/30 (23%) patients in the aMVAC group developed Grade 3 or 4 toxicity. Twenty percent of patients did not complete all four planed cycles of treatment and one patient (3%) did not proceed to surgery due to grade 4 sepsis. Of note, six patients (20.0%, 90% CI 9.1–35.7) developed renal insufficiency after neoadjuvant chemotherapy and 20/29 (69.0%, 90% CI 52.1–82.8) after surgery. Seventeen of 29 (59%) patients were cisplatin-ineligible after surgery due to renal function decline. These findings provide additional evidence favoring the use of chemotherapy in the neoadjuvant setting. A second carboplatin arm aimed to enroll patients with eGFR between 30 and 50 ml/min closed for poor accrual.

A second phase 2 multicenter single-arm trial evaluated split dosed neoadjuvant cisplatin (split 35 mg/m^2 on days 1 and 8) and gemcitabine (GC) in patients with cT2-T4a UTUC and baseline eGFR >55 ml/min [19]. Fifty-eight patients enrolled and 51 (89%) received a minimum of 3 chemotherapy cycles with 27 (47%) of them tolerating all 4 cycles. The trial met its primary endpoint with 36/57 (63%) achieving a pathologic stage <ypT2N0. Eleven patients (19%) had a complete response. The study also demonstrated encouraging survival data with a PFS of 78% (95% CI: 68–90) in 2 years and 65% (95% CI: 52–82) in 5 years ($P < 0.001$). Grade 3 or higher toxicities included lymphopenia in 19 (33%) patients, neutropenia in 18 (32%) patients and hyperglycemia in 8 (14%) patients. Thrombocytopenia, hypocalcemia, and febrile neutropenia ≥ grade 3 occurred in four (7%) patients.

The ongoing multicenter phase 3 randomized ECOG-ACRIN 8192 trial (NCT04628767) is assessing the efficacy and safety of neoadjuvant aMVAC with or without the checkpoint inhibitor durvalumab for patients with high grade UTUC.

Accurate clinical staging of the primary tumor is notably limited in UTUC, and hence true pathologic downstaging following receipt of NAC is difficult to

Table 1. Summary of prospective clinical trials for patients with UTUC

Phase	Study	Setting	Arm/intervention	UTUC / Total Participants	Primary endpoint	Result	Primary endpoint met?
UTUC-specific trials							
2	ECOG-ACRIN 8141[19]	Neoadjuvant (localized)	aMVAC (CrCl>50)	30/30 (100%)	pCR (ypT0N0)	4/29 (14%)	Yes
			GC (CrCl 30-50)	6/6 (100%)	pCR (ypT0N0)	3/6 (50%)	NA
2	GC[20]	Neoadjuvant (localized)	Split dose GC	58/58 (100%)	pCR (<ypT2N0)	11/58 (19%)	Yes
3	POUT[21]	Adjuvant (localized)	Platinum-based chemotherapy (cisplatin or carboplatin)	132/132	DFS	74.9% at 6 months	Yes
			Surveillance	129/ 129		60.3% at 6 months	
UC trials including patients with UTUC							
3	AMBASSADOR Alliance A031501[24]	Adjuvant (localized)	Pembrolizumab	81/354 (22.9%)	DFS; OS	DFS: 29.0 mo OS: 50.9mo	DFS: Yes OS: No[b]
			Observation	72/348 (20.7%)		DFS: 14.0 mo OS: 55.8mo	
3	CheckMate 274	Adjuvant (localized)	Nivolumab	74/353 (20.9%)	DFS	20.8 mo	Yes
			Placebo	75/356 (21.1%)		10.8 mo	
3	JAVELIN Bladder 100[26]	Advanced	Avelumab maintenance after 6 cycles of platinum chemotherapy without PD	244/350 (69.7%)	OS	21.4 mo	Yes
			Observation	269/350 (76.9%)		14.3 mo	
3	CheckMate 901[25]	Advanced	First-line platinum chemotherapy + nivolumab	33/304 (10.9%)	PFS; OS	PFS:7.9 mo OS:21.7 mo	Yes
			First-line platinum chemotherapy alone	44/304 (14.5%)		PFS: 7.6 mo OS:18.9 mo	
3	EV-301[36]	Advanced	Late-line EV	98/301 (32.6%)	OS	12.88 mo	Yes
			Late-line chemotherapy	107/307 (34.9%)		8.97 mo	
3	EV-302[35]	Advanced	First-line EV/P	135/442 (30.5%)	PFS; OS	PFS:12.5 mo OS:18.9 mo	Yes
			First-line chemotherapy	104/444 (23.4)		PFS:31.5 mo OS:16.1 mo	

[a]Closed due to poor accrual.
[b]Interim analysis.
aMVAC, accelerated methotrexate, vinblastine, doxorubicin, and cisplatin; GCa, gemcitabine, carboplatin; GC, gemcitabine, cisplatin; pCR, pathologic complete response; DFS, disease-free survival; OS, overall survival; PD, progression of disease; PFS: progression-free survival; EV, enfortumab vedotin; P, pembrolizumab.

distinguish from inherently low pathologic stage. Empirically offering NAC to all patients with high-grade UTUC may result in overtreatment for some patients; however, impaired postoperative renal function will preclude therapy to some with very high-risk disease. The new American Urological Association UTUC guidelines endorse NAC, especially for patients whose postoperative eGFR is expected to be lower than 60 ml/min or for those with other comorbidities that might preclude adjuvant chemotherapy [20]. Improvements in clinical staging and identification of novel biomarkers associated with cisplatin response may help better stratify patients to receive NAC vs. upfront RNU.

Adjuvant chemotherapy

Adjuvant platinum-based chemotherapy is the standard-of-care for eligible patients with high-risk, locally advanced UTUC who did not receive NAC. The POUT trial, a phase 3 open label, randomized controlled trial, was the largest published clinical trial of perioperative therapy in patients with non-metastatic UTUC [21]. The study enrolled 261 patients with pT2–T4N0–N3 UTUC with eGFR >30 ml/min and randomized them to either adjuvant platinum chemotherapy based on renal function or observation. Ultimately 126 patients received platinum-based chemotherapy with cisplatin or carboplatin and 95 (75%) completed 4 cycles. Disease-free survival (DFS) was significantly higher in the chemotherapy group and relative risk of disease recurrence or death 55% lower compared to the surveillance group [hazard ratio (HR): 0.45; 95% CI: 0.30–0.68; $P = 0.0001$]. At 5 year follow up, the DFS benefit was sustained and significantly higher in the chemotherapy group in the univariable but not the multivariable analysis with 67 events in the surveillance group and 50 in the chemotherapy group [22▪▪]. Adjuvant chemotherapy significantly improved OS after 5 years in the univariable analysis (HR: 0.68; 95% CI: 0.46–1.00; $P = 0.049$) but not in the multivariable analysis (HR: 0.76; 95% CI: 0.51–1.12; $P = 0.17$). Fifty-five (44%) of 126 patients in the treatment group experienced grade 3 or worse treatment-related adverse events, but there were no treatment-related deaths.

Despite the encouraging results of platinum-based chemotherapy in eligible patients, deterioration of renal function following nephroureterectomy may limit their ability to receive cisplatin [11]. In these cases, split-dose cisplatin or carboplatin in combination with gemcitabine have shown a promising safety profile in patients with eGFR< 50 mL/min and could present acceptable alternatives for patients who did not receive NAC [11,21,23].

Adjuvant immunotherapy

There are two FDA-approved immune checkpoint inhibitor monotherapies for patients with high risk UTUC who either had or were not eligible for perioperative chemotherapy: nivolumab and pembrolizumab.

Nivolumab

A phase 3 multicenter, double blind, randomized trial evaluated adjuvant nivolumab vs. placebo in patients who had undergone radical surgery for locally advanced UC at high risk of disease recurrence, regardless of prior receipt of NAC [24]. Three hundred fifty-three patients were randomized in the treatment group and 356 in the placebo group. UTUC patients were capped at approximately 20% to avoid overrepresentation.

The study met its primary endpoint with improvement in DFS in the intent-to-treat population, with a more substantial benefit for subjects with PD-L1+ tumors. 74.9% of patients in the nivolumab group and 60.3% of patients in the placebo group were disease free at 6 months (HR 0.70; 98.22% 95% CI: 0.55 – 0.90; $P < 0.001$). Grade 3–4 treatment-related side effects were reported in 17.9% of patients in the nivolumab group and in 7.2% of patients in the placebo group. Two treatment-related deaths occurred due to pneumonitis and 1 due to bowel perforation. A subgroup analysis showed that in the patients with UTUC, the apparent DFS benefit was not as strong as in the patients with primary bladder cancer. This subgroup analysis is hypothesis-generating, and important factors such as the receipt of NAC and extent of lymphadenectomy were not controlled for in this study. The use of adjuvant nivolumab in this high-risk population is guideline-endorsed without biomarker restriction.

Pembrolizumab

The phase 3, randomized AMBASSADOR Alliance trial assessed the efficacy of adjuvant pembrolizumab vs. observation in high-risk patients with UC following surgery [25▪]. The study demonstrated improved median DFS in the P group (29.0 vs. 14.0 months; HR: 0.69; 95% CI: 0.54–0.97; $P = 0.001$). No significant difference in interim median OS was demonstrated (50.9 vs. 55.8 months; HR: 0. 98; 95% CI: 0.76–1.26; $P = 0.884$). The study included 153/702 (21.8%) patients with UTUC and was not designed to asses outcome based on disease site.

SYSTEMIC THERAPY FOR METASTATIC UPPER TRACT UROTHELIAL CANCER

Platinum-based chemotherapy has been the standard or care for treating metastatic UC, including

UTUC, for decades. In recent years, emerging therapeutic classes including immunotherapy, antibody drug conjugates (ADCs) and targeted therapies have emerged as alternative treatment approaches to metastatic UC. Most of these agents are less nephrotoxic compared to traditional chemotherapy and therefore have relevance in patients with UTUC who may have decreased renal function at baseline or have a solitary renal unit due to prior nephroureterectomy.

Platinum combinations

Platinum-based chemotherapy has traditionally been the standard of care for patients with UTUC and bladder cancer. In 2023, a randomized phase 3 study compared the efficacy and safety of first line cisplatin-based chemotherapy with or without nivolumab in 608 patients with advanced UC, including 77 (12.7%) patients with primary tumors of the renal pelvis [26]. The study demonstrated improved median OS (21.7 vs. 18.9 months; HR: 0.78; 95% CI: 0.63–0.96; $P = 0.02$) and PFS (HR: 0.72; 95% CI: 0.59–0.88; $P = 0.001$) in the nivolumab group. The two regimens were relatively similar with regard to toxicity, with grade 3 or higher events in 61.8% and 51.7% of patients in the nivolumab and chemotherapy-only groups, respectively.

The phase 3, randomized JAVELIN Bladder 100 trial demonstrated median OS benefit (21 vs. 14.3 months; HR: 0.69; 95% CI: 0.56–0.86; $P = 0.001$) with the addition of maintenance avelumab vs. observation for patients who did not experience disease progression with frontline platinum/gemcitabine chemotherapy [27]. The study included 187/700 (26.7%) patients with UTUC randomized to the avelumab group. Even though both studies included UTUC and demonstrated survival benefit from the addition of immunotherapy to conventional chemotherapy in treating patients with advanced UC, they were not powered to UTUC patients specifically.

Enfortumab vedotin + pembrolizumab

Enfortumab vedotin (EV) is an ADC consisting of the microtubule disrupting agent MMAE linked to an antibody targeting Nectin-4 [28]. EV in combination with P received approval as first-line treatment for patients with locally advanced or metastatic UC, including UTUC, based on the results of the international, randomized, phase 3 EV-302 trial comparing EV/P with platinum-based chemotherapy [29,30▪▪]. EV-302 enrolled 442 patients in the EV/P group and 444 patients in the chemotherapy group, including 135 (30.5%) and 104 (23.4%) patients with UTUC, respectively. The study met its primary endpoint with longer PFS (12.5 months vs. 6.3 months; HR: 0.45; 95% CI: 0.38–0.54; $P < 0.001$) and OS (31.5 months vs. 16.1 months; HR: 0.47; 95% CI: 0.38–0.58; $P < 0.001$) in the EV/P group compared to the chemotherapy group. PFS and OS benefits were retained in the subset of patients with UTUC. EV/P demonstrated benefit among both cisplatin-eligible and ineligible patients.

EV monotherapy has also demonstrated benefit vs. late line chemotherapy in patients with metastatic UC who experienced progression with platinum-based chemotherapy and/or checkpoint inhibitors. Subgroup analysis in those studies demonstrated benefit for patients with UTUC who comprised approximately 30–40% of the study population [31,32].

Sacituzimab govitecan

Sacituzimab govitecan (SG) is an ADC targeting TROP-2, approved as late-line treatment for patients with metastatic UC. The ongoing phase 2 TROPHY trial is assessing the efficacy of SG and has demonstrated an overall response rate (ORR) of 27–32% in patients following platinum-based chemotherapy and/or immunotherapy [33,34▪]. Cohort 3, assessing the efficacy of SG combination with P, was also recently published, demonstrating an ORR of 41% [35▪]. Grade 3 or higher toxicity was seen in 35–87% of patients treated with single-agent SG and 61% of patients receiving SG/P. The number of UTUC patients included in those cohorts was not specified.

Biomarker-selected therapies

Currently two biomarker-selected therapies have been approved for metastatic UC: Erdafitinib and Trastuzumab Deruxtecan.

Erdafitinib

Erdafitinib is an oral FGFR1–4 inhibitor, currently approved for biomarker-selected patients with advanced UC. A randomized phase 2 international trial evaluated the use of erdafitinib in patients with advanced UC whose tumors harbored somatic *FGFR3* mutations or *FGFR2/3* fusions with disease progression following chemotherapy [36]. The study initially included three dosing groups and led to a 40% ORR in those treated. *FGFR3* alterations are more common in UTUC than in bladder cancer, and 23% of patients in the trial had UTUC with similar outcomes to those with bladder cancer. A long-term follow-up analysis with a median follow-up of 24 months demonstrated a response rate of 40% (95% CI: 30–49) [37]. Seventy-two (71%) of the 101 patients in the 8 mg continuous-dosing group reported grade 3 or higher treatment-related adverse

events, with the most common being stomatitis and hyponatremia. No treatment related deaths occurred.

In a randomized trial in patients with advanced UC following progression on a checkpoint inhibitor, compared to chemotherapy, erdaftininib led to superior OS (12.1 vs. 7.8 months) and PFS (5.6 vs. 2.7 months) [38]. In a separate phase III trial of edrafitinib compared to pembrolizumab in patients not previously treated with checkpoint inhibition, though the response rate was nearly double for erdafitinib, there was no difference in OS between these agents [39▪]. Both studies accrued approximately 33% of patients with UTUC.

In all of these studies, hallmark toxicities included hyperphosphatemia, stomatitis, skin and nail toxicity and gastrointestinal toxicity. Patients on erdafitinib need to be monitored for central serous retinopathy by an ophthalmologist [39▪]. As with EV, no specific trials for assessing the use of erdafitinib in UTUC exist. The efficacy of erdafitinib in UTUC should be further investigated since UTUCs are often luminal-papillary tumors with high FGFR3 expression [7,40].

Trastuzumab deruxtecan

In 2024 the HER-2 targeting ADC, trastuzumab deruxtecan, received FDA approval for patients with unresectable or metastatic solid tumors, including UC, based on the results of three trials: DESTINY-PanTumor02, DESTINY-Lung01, and DESTINY-CRC02 [41,42,43▪▪]. Of the 192 patients included in these trials, 41 had UC, with ORR 41.5%, median PFS 7.0 months (95%CI: 4.2–9.7) and median OS 12.8 months (95%CI 11.2–15.1). Approximately 18–25% of patients with advanced UC have HER2+ (2+ or 3+) tumors; however, investigating whether HER2 expression in UTUC differs from bladder UC remains an unmet need [44,45].

Though both the trastuzumab deruxtecan and sacituzumab govitecan studies allowed patients with UC, the number of patients with UTUC in each trial was not reported.

CONCLUSION

UTUC can be a challenging disease to manage, and many of its management principles are extrapolated from the bladder cancer literature. Cisplatin-based chemotherapy remains the standard of care in the perioperative setting, but issues related to nephroureterectomy and obstruction can impact renal function and eligibility for cisplatin in surgical candidates with high risk disease. Unique biological insights into UTUC pathogenesis and risk factors have expanded the therapeutic landscape for these patients. Emerging treatments for advanced and unresectable disease include less nephrotoxic regimens, which are particularly relevant in UTUC. Next-line therapy following EV/P has yet to be defined, but biomarker selection may inform more precise approaches in UTUC.

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NCCN Bladder Cancer.
AUA UTUC.
N.S.: None.

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