Upper Tract Neoplasms

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1. Introduction

Upper tract tumors refer to primary benign and malignant tumors occurring in the ureter and renal collecting system (pelvis, infundibula, and calyces). Urothelial carcinoma of the upper tract is termed **upper tract urothelial carcinoma (UTUC). Urothelial carcinoma (UC)** has replaced the previously commonly used and confusing term of transitional cell carcinoma, or TCC.

2. Keywords

Urothelial Carcinoma, Upper Tract Urothelial Carcinoma, Nephroureterectomy, Endoscopic Management

3. Risk Factors and Pathophysiology

The **majority (90%) of upper tract malignancies are of urothelial origin, while squamous cell carcinoma, adenocarcinoma, and small cell cancer** are much less common. **Benign tumors of the upper tract** include: **fibroepithelial polyps** (the most common benign tumor of the upper tract), **inverted papillomas, fibromas, and von Brunn's nests**. The major associated risk factors for UTUC are **environmental toxins** (**Table 1**). Tobacco is the primary dose-dependent risk factor, accounting for 25–60% of UTUC.

Patients with primary bladder cancer are at risk of developing UTUC. Although the risk of upper tract recurrence after primary bladder cancer was historically thought to be between 2% and 7%, contemporary studies indicate that the risk may be as low as 0.8%.[1,2] In a meta-analysis of 22 studies evaluating the risk of UTUC after bladder cancer, the greatest attributable risks are related to patient- and tumor-related factors associated with longer overall survival, such as low grade and non-invasive stage, with resultant increased time during which a patient is at risk for upper tract recurrence. **Furthermore, given that urothelial carcinoma is thought to be a pan-urothelial disease (reflecting a field change defect), multifocality and CIS are associated with a 3-fold and 2-to-4-fold increased risk of UTUC recurrence, respectively**.[3]

The usage of double J ureteral stents prior to radical cystectomy has been suggested as a potential modifiable risk factor for future upper tract recurrence, presumably related to

increased risk of urinary reflux.[4] This had led some authors to recommend preferential use of percutaneous nephrostomy tubes over internalized ureteral stents in patients with bladder cancer in patients with ureteral obstruction.

Recently, the increase in risk of UTUC associated with exposure to **aristolochic acid has been described**. Aristolochic acid is a mutagen found in *Aristolochia clematitis* and related plants (commonly known as bladderworts), which are found in Eastern Asian (China, Taiwan, Vietnam, India) herbal remedies. *Aristolochia* also grows in wheat fields in the tributaries of the Danube River. Aristolochic acid toxin causes nephropathy as well as UTUC, and has been shown to be the major causative factor in **Balkan nephropathy**, as well as Chinese and Taiwanese herbal nephropathy.

Other known risk factors for pharmacologic nephropathy include **analgesic overuse or abuse, exposure to phenacetin** (banned) and **cyclophosphamide**.

An under-appreciated association is the link between UTUC and **Lynch syndrome (hereditary non-polyposis colon cancer)**. **The prevalence of UTUC in patients with Lynch syndrome is 3-28%**. Recognition of this entity by urologists is of paramount importance as they may serve as the initial point of contact for patients and identify affected individuals for appropriate screening. **An UTUC patient with a personal or family history of colon, small bowel, sebaceous, endometrial, or ovarian cancer should raise the suspicion for Lynch syndrome and prompt a referral for genetic evaluation**. In particular, patients (especially males) with known ***MSH2*** pathogenic variants or family history of Lynch syndrome-associated UTUC appear to be at increased risk for harboring UTUC. The National Comprehensive Cancer Network (NCCN) guidelines (Genetic/Familial High-Risk Assessment: Colon Cancer; version 1.2021) section on Lynch syndrome states " **consider tumor screening for mismatch repair (MMR) deficiency in urothelial carcinomas regardless of age**." Initial screening tests performed on **tumor tissue** (somatic testing) consist of immunohistochemistry looking for loss of MMR proteins and microsatellite instability analysis, as over 90% of Lynch syndrome cancers have high microsatellite instability and/or lack expression of at least one of the MMR proteins. If found, germline testing for a deleterious mutation in MLH1, MSH2, MSH6, and PMS2 or EPCAM gene is required to establish the diagnosis of Lynch syndrome.

In patients with Lynch syndrome, routine surveillance for urothelial carcinomas is not supported by data. **Surveillance may be considered in selected individuals such as with a family history of urothelial carcinoma**. Individuals with **MSH2** pathogenic variants (especially males) appear to be at higher risk. Despite a lack of evidence, various surveillance schedules and schema have been described, but there is insufficient evidence to recommend a particular strategy. One option may include an annual urinalysis beginning at age 30-35,[5] however even this strategy has been called into question. Routine use of urine cytology is not recommended due to low sensitivity and specificity.[6] Many patients with Lynch syndrome already undergo imaging for follow-up of a treated Lynch syndrome-associated malignancy.

The molecular basis of UTUC is under active investigation, resulting in many observations that are revealing of the biology of this disease. **While bladder cancer and UTUC are frequently treated**

similarly, the molecular and genetic pathophysiology of the two diseases are surprisingly different. For example, high-grade bladder cancer and high-grade UTUC demonstrate a similar spectrum of genetic alterations, however the frequencies are different.[7,8] **High-grade UTUC more commonly harbors alterations in FGFR3, HRAS, CDKN2B** compared with high-grade bladder cancer. **While *FGFR3* alterations were common in all UTUC, *p53* mutations were exclusively seen in high-grade disease**. A more recent report elucidated the relationship between FGFR3 expression, dampened interferon gamma response genes, and a T-cell depleted immune signature.[9] They also demonstrate that most **UTUC tumors are more closely related to luminal-papillary molecular subtypes seen in bladder cancer**. Finally, despite significant dysregulation of DNA damage response genes, **UTUCs have lower tumor mutation burden than their bladder cancer counterparts**.

References 10,11,12,13,14,15,16,17

Table 1. Risk Factors For Upper Tract Urothelial Carcinoma
Smoking
Bladder cancer (CIS, multifocality, proximity to ureteral orifice)
Lynch syndrome (especially with *MSH2* mutations)
Aristolochic acid (Balkan nephropathy, Chinese and Taiwanese herbal nephropathy)
Arsenic
Analgesics
Occupational exposure (petroleum, plastic, coal, tar, dyes)
Chronic inflammation and infection
Cyclophosphamide

Table 2. Clinical Signs and Symptoms of Upper Tract Urothelial Carcinoma
Hematuria (75-82% of cases)
Flank pain
Dysuria
Symptoms of advanced disease related to metastases (Common sites of metastases include liver, lungs, bones, and regional lymph nodes)

Table 3. Clinical Staging of Upper Tract Urothelial Carcinoma
Tx: tumor invasion cannot be assessed
Tis: carcinoma in situ; for UTUC generally accepted as a **positive selective cytology in the absence of visible tumor**. However, CIS may coexist with papillary and sessile tumors.
Ta: noninvasive on biopsy
T1: invasion of lamina propria on biopsy
T2: invasion of muscularis; however, this is typically not seen on biopsy nor on imaging thus is rarely if ever documented
T3: invasion of periureteral fat, renal parenchyma, or renal sinus fat; seen on imaging only and not on biopsy
T4: invasion of adjacent organs; seen on imaging only.
N0: no involvement of lymph nodes on imaging
N1 (or N+): involvement of lymph nodes on imaging.

4. Epidemiology

UTUC comprises only 5–10% of all UC. The incidence is increasing with the largest increase seen with carcinoma-in-situ tumors. **The majority of patients (60–65%) with UTUC present with higher stage disease** compared to patients diagnosed with bladder cancer. Patients with UTUC are diagnosed at an older age than those with bladder cancer, and age is independently associated with inferior survival.

The gender disparity is less significant with UTUC than in bladder cancer, with a ratio of 2:1 male to female (vs. 4:1 in bladder cancer), and gender does not appear to be associated with oncologic outcomes. Racial disparities have been observed, including increased risk of mortality in non-Hispanic African American men. There is controversy regarding prognosis based on tumor location (renal pelvis vs ureter), but generally stage-for-stage, outcomes are similar for renal pelvis and ureteral cancers.

References 14,18,19,20,21,22

5. Diagnosis and Evaluation

5.1 Diagnosis

A suspicion for UTUC is raised by signs, symptoms, hematuria, or incidentally noted imaging (e.g. a filling defect on delayed images following CT or MRI with contrast, hydronephrosis). Occasionally patients are found to have a positive cytology in the setting of a negative evaluation of the bladder with cystoscopy. The diagnosis is made with a combination of endoscopy (commonly retrograde ureteroscopy, occasionally percutaneous antegrade pyeloscopy/ureteroscopy) and cross-sectional or retrograde imaging. **A calyceal, renal pelvic, or ureteral filling defect on delayed images of contrast-enhanced studies is considered a UTUC until proven otherwise**. Direct visualization is necessary to rule out other etiologies which can result in a filling defect, such **as blood clots, radiolucent stones, sloughed papillae or mucosal folds**.

5.2 Evaluation

(see **Table 2**)

Evaluation consists of **cystoscopy, retrograde pyelogram, and ureteroscopic evaluation with biopsy and selective washings**. Selective washings in addition to biopsy can provide additional information, and **in the absence of a solid tumor, a positive selective cytology raise concern for CIS**, which is difficult to diagnose on the often miniscule biopsies obtained at ureteroscopy.

5.2.1 Cross-Sectional Imaging/Laboratory Testing

If not obtained at time of diagnosis, cross-sectional imaging is indicated for staging and assessment of lymphadenopathy and metastases. **Computed tomographic urography (CTU)** has replaced intravenous pyelography (IVP) as the study of choice. **Magnetic resonance urography (MRU)** is an

excellent alternative in patients with iodine allergy or poor renal function. **However, cross-sectional imaging has suboptimal sensitivity for characterizing stage (local invasion)**. A **retrograde pyelogram** is used for any non-visualized areas of the collecting system or for additional documentation. **Chest imaging** is indicated to evaluate for metastatic disease. **Bone scans** are obtained if there is clinical suspicion for bone metastases.

Laboratory studies usually obtained include **serum creatinine** and estimates of **glomerular filtration rate, liver function tests** (which provide an indirect indicator for liver metastasis), **alkaline phosphatase, urinary cytology, and culture. A nuclear medicine renogram** may be obtained to assess for differential renal function to assess the relative contribution of the ipsilateral renal unit to the patient's global renal function.

5.2.2 Role of Cytology and Other Markers

A positive urinary cytology in the presence of a negative cystoscopy significantly raises the possibility of UC in sites other than the bladder such as the prostatic urethra or upper urinary tracts (i.e. UTUC), and warrants upper tract evaluation[23] and consideration for enhanced cystoscopy (e.g. with blue light) if available. **In those with confirmed UTUC, selective washings with a positive cytology are associated with higher stage disease**. Other markers, such as fluorescence in-situ hybridization (FISH), NMP-22, among others, are still preliminary, may be costly, and their role in the evaluation of UTUC remains undefined.

5.2.3 Grading and Staging

(see **Table 3**)

Accurate grading and staging of UTUC is notoriously challenging and limited by the quality of the endoscopic biopsy equipment available. **Tumors are graded according to the World Health Organization criteria for urothelial carcinoma of the bladder into low-grade and high-grade disease.** Using ureteroscopic biopsy and current cross-sectional imaging, one cannot reliably discern invasive disease given that biopsies are frequently too small to sample deeply enough to adequately assess the ureteral wall for invasion and imaging does not have enough resolution for the thin-walled upper tract muscular wall. Thus, **most tumors are staged as cTx.**

5.2.4 Risk Stratification

Risk stratification is important to help determine whether patients may be fit for organ-sparing treatment or whether radical nephroureterectomy is warranted. The European Association of Urology has delineated low-risk and high-risk groups based on commonly available preoperative variables (**Table 4**[24]). All of the low-risk variables need to be present for a patient to be considered low-risk and therefore potentially amenable to endoscopic treatment. **If any high-risk variables are present, then the patient is considered high-risk**.

Table 4. Proposed risk classification by the European Association of Urology[24].

Risk category	Variables
Low-risk UTUC	Unifocal disease Tumor size <2cm Low-grade cytology Low-grade URS biopsy No invasive aspect on CTU
High-risk UTUC	Hydronephrosis Tumor size >2cm High-grade cytology High-grade URS biopsy Multifocal disease Previous radical cystectomy for bladder cancer Variant histology

6. Organ-Sparing Treatment

Organ-sparing treatment may be warranted in patients with compromised renal function or a solitary kidney. Generally, **organ-sparing treatment is reserved for patients with low-risk disease**. This approach combines endoscopic treatment, often with **ureteroscopic laser ablation or percutaneous resection of all visible tumor, with or without adjuvant intraluminal therapies such as BCG or cytotoxic chemotherapy** (e.g. mitomycin-C, gemcitabine). The OLYMPUS trial also demonstrated the ability of **thermosensitive hydrogels for chemoablation of limited volume low-grade tumors**.[25] Segmental ureterectomy with urinary reconstruction may also be considered. **Patients who undergo organ-sparing treatment warrant close follow-up for ipsilateral recurrence with routine urinalysis, urine cytology, ureteroscopy, and cross-sectional imaging.**

6.1 Endoscopic Treatment

Patients with **low-risk tumors** that are **accessible via endoscopy** may be **managed with laser ablation** using flexible ureteroscopy with the goal of complete ablation/removal. A systematic review and separate meta-analysis demonstrated equivalent overall survival in patients treated with this approach, although studies are mainly from institutional case series with known selection bias.[26,27]

6.2 Intraluminal Therapy

Intraluminal therapy for UTUC is challenging given prompt drainage of instilled fluid in an unobstructed upper tract, with limited dwell time of the therapy resulting in relatively short contact time between tumor and therapeutic agent. Until recently, the three primary methods to deliver intraluminal agents to the upper tracts were **(1) antegrade via percutaneous nephrostomy tube, (2) retrograde via a ureteral catheter, or (3) retrograde via passive reflux with an indwelling ureteral stent** . One study found that retrograde instillation via an open-ended ureteral catheter resulted in the highest mean percent surface area stained in an ex vivo pig model.[28] Additionally, there is concern that pyelovenous backflow in the kidney can result in higher systemic absorption of agents and potentially result in higher rates of side effects, such as sepsis from BCG and myelosuppression from cytotoxic chemotherapy.

The challenges in achieving a prolonged dwell time in the upper urinary tract for traditional liquid agents led to interest in the use of **reverse thermosensitive hydrogel polymers** as a means for improving intraluminal therapy for the upper tract. These hydrogels exist in a viscous liquid state at cold temperatures, but rapidly form a gel at body temperature, allowing them to be instilled into the upper tract in the cold liquid state, where they warm and gelatinize, thereby prolonging contact time between the therapeutic agent and the at-risk urothelium. In the upper urinary tract, urine production causes gradual dissolution over 4–6 hours. **Jelmyto™ is a mitomycin-C-containing hydrogel which was approved by the FDA in April 2020 for the treatment of low-grade UTUC** based on the findings of the OLYMPUS trial.

The **OLYMPUS trial was a phase 3, multicenter, single-arm prospective clinical trial in patients**

with at least 1 measurable low-grade papillary tumor ≤1.5cm and no suspicion for high-grade disease.[25] Given that these patients had known existing disease at the time of treatment, this trial evaluated the ability of Jelmyto™ to chemoablate existing tumors, rather than assessing its efficacy as a purely adjuvant therapy. In total, 48% of patients had tumors deemed unreachable by laser at baseline. Patients enrolled in the trial received 6 weekly retrograde instillations of Jelmyto™, followed by ureteroscopic evaluation, urine cytology, and for-cause biopsies 4–6 weeks after the last instillation, at which point complete response was evaluated as the primary outcome. A total of 71 patients received at least 1 instillation of Jelmyto™, with a **complete response rate of 59%** (95% CI 47–71%) and an 11% partial response rate. A subset of these complete responders (n=20) underwent monthly maintenance treatments and an evaluation at 6, 9, and 12 months, of whom 14 (70%) had a continued complete response. Adverse events were common, with more than 40% of patients experiencing a ≥ grade 3 adverse event. **The most commonly reported adverse events were ureteral stenosis (44%), urinary tract infection (32%), hematuria (31%), flank pain (30%), and nausea (24%)**.

Due to the burdensome nature of weekly retrograde instillation of Jelmyto™, (usually in clinic with fluoroscopy), initial attempts at antegrade instillation via a percutaneous nephrostomy catheter have been published.[29] This approach may also have the potential to reduce the most concerning adverse event—ureteral stenosis.

6.2.1 Intraluminal Bacillus Calmette Guerin (BCG)

Rationale: **BCG is the most common intraluminal agent used as primary treatment** (for CIS) **and as adjuvant therapy** (after endoscopic eradication of all visible tumor burden). Mechanisms of action involve both the innate and adaptive immune system activation, as well as a direct cytotoxic effect on tumor cells.[30]

Outcomes: The efficacy for treating CIS (Risk of recurrence: 40%, progression: 5%) in the upper urinary tract appears to be similar to that seen in the bladder[31] while the efficacy for treatment of Ta/T1 lesions is lower (Risk of recurrence: 59%, progression: 41%). The benefit of adjuvant BCG in the setting of non-CIS UTUC is unclear, however intraluminal BCG is included as an option for the management of low risk UTUC of the renal pelvis in the current **NCCN guidelines**.

Adverse Effects: Similar to the experience with urinary bladder, BCG instillation in UTUC has been associated with **urosepsis** (typical bacterial and TB) and flu-like symptoms after infusion. Furthermore, the pyelovenous backflow from pressurized upper tract instillation of BCG may contribute to increased rates of systemic BCG side effects thereby limiting its utility in this setting.

6.2.2 Intraluminal cytotoxic chemotherapy

Rationale: **Mitomycin-C** is the most commonly used chemotherapeutic agent for intraluminal instillation for UTUC (although **gemcitabine** is increasingly used due to comparable efficacy, decreased cost and toxicity in the low and intermediate risk bladder cancer populations).[32]

Outcomes: While intraluminal chemotherapy such as mitomycin-c appears to be safe and well

tolerated, its benefit when delivered in the aqueous state in UTUC remains unclear. The OLYMPUS trial demonstrated that **when delivered as part of a thermosensitive hydrogel, mitomycin-c has the ability to chemoablate limited-volume low-grade tumors in more than half of treated patients at the 3-month timepoint**.[25] It is thought that patients with low-intermediate risk disease may have the most to gain from Mitomycin C instillation, as extrapolated from the bladder experience, but this has not been proven or disproven for UTUC. Low dose BCG with interferon-alpha and gemcitabine are two other available options with limited published experience.

Adverse Effects: Adverse effects of Mitomycin C include **systemic absorption with ensuing hematologic effects, rare cases of urothelial necrosis, and contact dermatitis**. When delivered repeatedly as part of a hydrogel polymer, **ureteral stenosis was observed in 44% of patients**. Whether this was due to the drug itself or the repeated instrumentation of the ureter is not known.

Reference 33,34,35,36,37,38,39,40

6.3 Segmental Ureterectomy

Indications: Of the organ-sparing options for low-risk UTUC, **segmental ureterectomy is perhaps one of the simplest to perform but must be utilized with caution**. The aim of segmental ureterectomy is to remove a diseased portion of ureter and re-anastomose the remaining ureter with or without the need for additional reconstruction. It is best suited to **small, unifocal ureteral tumors not amenable to ureteroscopic management. Lower ureteral tumors can be managed by distal ureterectomy and vesicoureteral reimplantation with Psoas hitch or Boari flap if indicated to ensure a tension-free repair. Higher ureteral tumors can be managed by segmental ureterectomy and primary ureteroureterostomy or ureterocalicostomy in appropriate renal units**.

Operative Considerations: Distal ureterectomy is traditionally performed through either an open, laparoscopic or robot-assisted laparoscopic approach. The distal ureter is dissected beyond the bifurcation of the iliac vessels. Direct contact with the tumor is avoided through proximal (and distal if possible) ligation of the ureter and concomitant excision of a cuff of bladder encompassing and surrounding the ipsilateral ureteral orifice. Ureteral re-implantation is performed, often with a **psoas-hitch with or without a Boari flap** if extensive length is lost from segmental ureterectomy to ensure a tension-free anastomosis. Division of the contralateral lateral pedicle is more easily accomplished using a midline incision rather than a Gibson type incision if performing an open approach. However, this operation is particularly facilitated by the robotic approach. **For both segmental and distal ureterectomy, intraoperative frozen sections of the proximal segment of the ureter should be considered**. In case of intraoperative positive margins, the proximal end of the ureter is re-resected until frozen sections are negative. **Resection of the entire distal ureter, ureteral orifice, and surrounding bladder cuff is a key element of both nephroureterectomy as well as distal ureterectomy**. The surgeon needs to exercise due diligence in visually confirming complete resection as well as **preventing spillage of tumor cells** by whatever approach is chosen. Reconstruction via spatulated uretero-ureterostomy, ureterocalicostomy, or ureterovesicostomy, as

indicated, is **generally performed over an internalized double-J stent and the operative site is drained. Regional lymphadenectomy should be considered for prognostic and possibly therapeutic purposes**.

Outcomes: Retrospective data suggests equivalent long-term oncologic outcomes achieved in patients treated with segmental ureterectomy compared with those treated with nephroureterectomy. Notably, the ipsilateral upper urinary tract remains at an increased risk of UTUC relapse (5–15%) and should be periodically monitored accordingly.

Complications: **Complications unique to segmental ureterectomy include ureteral stricture formation (2–10%), and post-operative urine leak**.

References 41,42,43

7. Radical Nephroureterectomy

Indication: High-grade UTUC and low-grade UTUC, where nephron-sparing options are not feasible or are not oncologically appropriate due to tumor volume or multifocality.

Operative Considerations: Radical nephroureterectomy (RNU), by either open, laparoscopic, or robotic means, requires complete removal of the kidney with surrounding **Gerota's fascia, entire ureter, and a bladder cuff**. The ureter is traditionally clipped early, often before hilar control, to prevent disrupted tumor from spilling into the bladder. The bladder cuff should include the entire ureteral orifice with a cuff of surrounding urothelium. **The adrenal gland is generally spared unless tumor involvement of the upper pole raises concern for adrenal involvement**. Following RNU and bladder closure, after confirming that the vesicorraphy is water-tight, perioperative intravesical chemotherapy (e.g. mitomycin-C, gemcitabine, pirarubicin) is associated with a decreased risk of recurrence within the bladder [44,45]) (**see section 7.3** for further discussion).

The role of **lymphadenectomy at the time of RNU** has been investigated in several retrospective studies and is recommended in patients with high-risk disease. A randomized clinical trial to assess the therapeutic benefit of lymphadenectomy at the time of RNU is currently recruiting. Based on data from retrospective studies, **template-based lymph node dissection should be considered as an adjunct to nephroureterectomy and partial ureterectomy in patients with high grade UTUC**. The number of lymph nodes removed has achieved independent predictor status for cancer-specific and all-cause mortality.[46] Retrospective data suggest that **at least eight lymph nodes** should be removed to ensure a true likelihood of having pN0 status.

Outcomes: In one of the largest RNU series reported to date, the 5-year recurrence-free and cancer-specific survival probabilities were 69% and 73% respectively. This included patients with both low- and high-grade UTUC.

Complications: Complications specifically after RNU have not been well documented, but likely parallel those observed after radical open or laparoscopic renal surgery. Additional considerations include lymphatic leaks in cases when a lymph node dissection is performed, and urinary

extravasation from the cystotomy site.

References 47,48,49,50

7.1 Neoadjuvant Chemotherapy

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Rationale: Neoadjuvant chemotherapy is presumed to play an important role in invasive UTUC, extrapolating from the bladder cancer literature. **The enthusiasm for chemotherapy before nephroureterectomy for UTUC arises from the fact that, following surgery, the majority of patients' renal function will decline, rendering a significant proportion ineligible for cisplatin-based therapy**. Thus, presurgical therapy capitalizes on a patient's maximal renal function for optimal multimodality therapy

Outcomes: Retrospective data suggests a benefit with neoadjuvant cisplatin-based chemotherapy prior to RNU, with a recent study showing a 15% rate of pT0 disease and significant down-staging.[51,52,53] **Cisplatin-based multi-agent chemotherapy regimens, such as Gemcitabine plus cisplatin (GC) or methotrexate, vinblastine, Adriamycin, and cisplatin (MVAC) are preferred**. The first prospective intergroup study of **neoadjuvant dose dense MVAC prior to nephroureterectomy in patients with high grade UTUC (ECOG-ACRIN 8141) demonstrated complete pathologic response rate of 14% and a 62% rate of < pT2 disease**.[54] In this study, chemotherapy was well tolerated without significant increase in surgical morbidity, establishing the neoadjuvant paradigm as a viable strategy in high-risk UTUC. Several other trials are currently underway to evaluate this prospectively (NCT01261728). As immunotherapy with checkpoint inhibitors migrates to earlier disease stages, the role of immunotherapy as neoadjuvant therapy in patients with UTUC is being evaluated. For example, one study is evaluating the combination of durvalumab and tremelimumab in patients with high-risk muscle-invasive urothelial cancer who are ineligible for neoadjuvant chemotherapy (NCT02812420).

Adverse Effects: Commonly used chemotherapy agents are listed below in **Table 5** along with the mechanism of action and the common side effects.

Table 5.

Chemotherapy agent	Mechanism of action	Common adverse effects
Gemcitabine	Antimetabolite, pyrimidine analog	Peripheral edema (20%), Nausea and vomiting (69%), Proteinuria (45%), hematuria (35%), anemia (68%), Neutropenia (63%), Thrombocytopenia (24%), Transaminitis (55–68%), Skin rash (30%), Alopecia (15%), Stomatitis (11%)
Cisplatin	Alkylating agent	Nausea and vomiting (76–100%), Nephrotoxicity (28–36%), Anemia (<40%), Leukopenia (25–30%), Thrombocytopenia (25–30%), Ototoxicity (10–31%), Neurotoxicity (dose and duration dependent)
Carboplatin	Alkylating agent	Vomiting (65–81%), Abdominal pain (17%), Hyponatremia (29–47%), Hypomagnesemia (29–43%), Hypocalcemia (22–31%), Hypokalemia (20¬–28%), Anemia (71–90%), Leukopenia (85%), Neutropenia (67%), Thrombocytopenia (62%), Decreased creatinine clearance (27%)
Methotrexate	Antimetabolite, antifolate	Cardiovascular, Central nervous system, Alopecia (<10%), Burning sensation of skin (3–10%), Skin photosensitivity (3–10%), Diarrhea (<10%), Nausea and vomiting (<11%), Stomatitis (2–10%), Thrombocytopenia (3–10%), Leukopenia

		(1–3%), Transaminitis
Vinblastine	Antimicrotubular, vinca alkyloid	Hypertension, Malaise, Alopecia, Anemia, Granulocytopenia, Leukopenia, Ostealgia, Jaw pain
Adriamycin	Topoisomerase II inhibitor	Cardiac, Malaise, Alopecia, Leukopenia (<75%), Neutropenia (<75%), Anemia, Thrombocytopenia
Table adapted from Uptodate.com		

References 55,56,57,58

7.2 Adjuvant systemic therapy

Rationale: Patients with invasive UTUC following definitive local therapy (nephroureterectomy/distal ureterectomy) are at high risk for disease recurrence. Both the lack of high-level data (trials pending) and challenges in staging lead clinicians to more frequently recommend surgery over neoadjuvant therapy. Data from a **phase III trial (POUT) demonstrated that adjuvant chemotherapy consisting of 4 cycles of gemcitabine-cisplatin (gemcitabine-carboplatin if GFR 30–49 ml/min) resulted in improved progression-free survival compared to surveillance**.[59]

Outcomes: This is the first randomized controlled trial powered to demonstrate a difference in disease-free survival in patients with pT2–4 N0–3, M0 UTUC following definitive surgical therapy. This trial met early stopping rules for enrollment because the primary endpoint was achieved. At a median follow-up of 30.3 months, adjuvant chemotherapy was associated with significant improvement in disease-free survival (hazard ratio 0.45 and a lower risk of metastasis or death (hazard ratio 0.48).[60]

Updated data presented at ASCO 2021 (median follow-up 48 months) demonstrated continued improved disease-free (HR 0.51) and overall survival (HR 0.52). With regards to overall survival, adjuvant chemotherapy was associated with a 30% reduction in risk of death although this did not meet statistical significance (p = 0.09).

While the authors recommended adoption of adjuvant chemotherapy following RNU as the standard of care, this study did not compare neoadjuvant to adjuvant therapy. Additional analyses will need to be performed to understand differences in response by stage. It is unclear how many patients could have been offered neoadjuvant chemotherapy but became ineligible for systemic therapy (especially cisplatin-based chemotherapy) after nephroureterectomy.

Several trials have evaluated the use of checkpoint inhibitors in the adjuvant setting for patients with urothelial carcinoma at high-risk of recurrence following resection. The majority of patients in these trials had urothelial carcinoma of the bladder, however a subset included patients with upper tract disease. The IMvigor010 trial evaluate atezolizumab versus observation in patients with muscle-invasive or node-positive disease at cystectomy or nephroureterectomy. The trial failed to meet its endpoint of improved disease-free survival.[61] More recently **the CheckMate 274 study evaluated adjuvant nivolumab in a similar setting. This study, which was double-blinded and placebo-controlled, demonstrated that nivolumab improved the proportion of patients disease-free at 6 months from 60.3% to 74.9%, improving median disease-free survival from 10.8 to 20.8 months.** [62] Only 20% of the study cohort had upper tract disease, and on subset analysis the benefit of nivolumab did not appear to apply to the upper tract subset, however the study was not powered to demonstrate an improvement in this subset of patients, and so further study will be required to evaluate efficacy in patients with UTUC. Based on these findings, **Nivolumab is now FDA approved for this indication, and will be an option for patients following**

nephroureterectomy at high risk of recurrence. This indication will be particularly relevant in those who are not eligible for chemotherapy.

The **PROOF 302 trial is an ongoing placebo-controlled phase 3 adjuvant study to evaluate the efficacy of infigratinib--an oral targeted FGFR1-3 inhibitor--after nephroureterectomy or segmental ureterectomy for patients with high risk UTUC and specific FGFR3 genetic alterations (NCT04197986).** To be eligible, patients who have received neoadjuvant chemotherapy need to have significant residual disease on final pathology (≥ ypT2 and/or yN+). Patients who have not received neoadjuvant chemotherapy must be ineligible for adjuvant chemotherapy or refuse cisplatin-based adjuvant chemotherapy and have the following pathologic features: ≥ pT2 pN0–2. The primary endpoint is disease-free survival, and the trial is expected to conclude in 2024.

Adverse Effects: **See subsection 7.1 Neoadjuvant chemotherapy for a Table of common chemotherapy agents and associated side effects**.

References 63

7.3 Preventing bladder recurrences after nephroureterectomy

Two randomized prospective studies have shown a significant reduction in bladder cancer recurrence after nephroureterectomy using intravesical therapy with highly favorable safety profiles. A Cochrane review based on the available literature suggests a benefit in recurrence rates (**HR 0.51 with a single instillation of chemotherapy post-operatively**) however the impact on overall survival remains undefined and the quality of the available evidence is low. Nevertheless, based on these studies, **intravesical instillation of an approved chemotherapeutic agent (such as mitomycin-C or gemcitabine in the USA) after nephroureterectomy and before catheter removal should be utilized** . In these randomized trials, intravesical therapy was administered before urinary catheter removal in the immediate postoperative period (usually on postoperative day 1). A cystogram to rule out bladder leakage from the cystotomy site may be considered prior to instillation.

References 64,65

8. Treatment of Metastatic UTUC

Rationale: The cornerstone of systemic therapy for metastatic urothelial carcinoma of the upper tract is **cisplatin-based cytotoxic chemotherapy**. **Cisplatin eligibility** requires adequate baseline renal function and absence of comorbidities such as pre-existing neuropathy and hearing loss, among others **. A cisplatin-based combination chemotherapy regimen, such as gemcitabine plus cisplatin (GC) or dose-dense methotrexate, vinblastine, adriamycin, and cisplatin (ddMVAC) are preferred**.

Cisplatin-ineligible patients may be treated with gemcitabine and carboplatin, or an immune checkpoint inhibitor (ICI) . The receptor programmed cell death-1 (PD-1) is expressed on T- and B-cells, as well as cells of the innate immune system, and bind to the endogenous ligands

programmed cell death ligand-1 and -2 (PD-L1/2). **PD-L1/2 is also expressed on immune cells and binding with PD-1 results in immune tolerance and dampening of the immune response. Tumors cells can express these molecules thus resulting in suppression of anti-tumor immunity. Blocking this interaction with ICIs can result in a vigorous anti-tumor immune response**.

ICIs first gained FDA approval in 2016, and since several other ICIs have subsequently been approved.[66] **Atezolizumab, Durvalumab, and Avelumab are PD-L1 inhibitors, and Pembrolizumab and Nivolumab are PD-1 inhibitors. Patients can receive a first-line ICI if they are cisplatin-ineligible or if the tumor stains positive for PD-L1** (percentage staining required and assay used varies). **For patients who progress after first line cytotoxic chemotherapy for advanced or metastatic urothelial carcinoma, including UTUC, second line options include Nivolumab, Pembrolizumab, Avelumab and other cytotoxic chemotherapy regimens (such as combinations of ifosfamide, metrotrexate, doxorubicin, paclitaxel).**

Additional third line agents now include Erdafitinib (the first targeted therapy based on FGFR mutations), and the drug-antibody conjugate, enfortumab vedotin.[67]

Outcomes: **Response rates with cytotoxic chemotherapy in patients with metastatic UTUC in the first-line setting are 20–60%.** Unfortunately, durable complete responses are rare (<5%). Following cisplatin, historical response rates approached 10% while, treatment with CPI results in response rates between 13% and 21%.

Adverse Effects: The adverse effects from standard cytotoxic chemotherapy was reviewed previously in **Table 5** of Subsection 7.1 Neoadjuvant Chemotherapy.

Immunotherapy with CPIs has a distinct set of adverse reactions that stem from its mechanism of action, namely unleashing of the immune system, which leads to several typical immune related adverse events (irAEs) that resemble autoimmune diseases.[68] The **most common irAEs include colitis, endocrinopathies, nephritis, liver toxicity, skin rash or pruritis, and pneumonitis**, but can include many others. **Table 6** includes the common irAEs for each CPI. Treatment includes early diagnosis and cessation of therapy with steroid treatment in severe cases.

Table 6. Adapted from Martins et al.[68]

Immunotherapy agent	Line of treatment	Target	Any grade (grade>=3) immune-related adverse event
Avelumab	2L Post-platinum	PD-L1	Diarrhea 7–10% (0%), Pulmonary 1% (0–1%), Rash 13% (0%), Neurological 1% (1%), Endocrinopathy 7% (0%), Hepatic 1.6–6.8% (1.1–2%), Renal 1% (0%)
Pembrolizumab	1L cisplatin ineligible, 2L post-platinum	PD-1	Diarrhea 6–19.1% (0–1%), Colitis 1–3.7% (0.3–2%), Pulmonary 4–5% (0.8–2%), Rash 9–16.1% (0.2–0.3%), Endocrinopathy 15–23.4% (1–2%), Hepatic 0.3–1.8% (0–1.4%), Renal 0.4% (0.4%)
Nivolumab	2L Post-platinum	PD-1	Diarrhea 8–16% (1%), Colitis 1% (0.3–0.5%), Pulmonary 1.5–4.9% (0–1.4%), Rash 9–15% (0.5–3.5%), Neurological 0.3% (0.3%), Endocrinopathy 7.3–10.5% (0–1%), Hepatic 3.4–10.8% (1.4–1.5%), Renal 1.9–2.0% (0–0.5%)

References 69,70,71,72

9. Radiation Therapy

The role of radiotherapy in UTUC has not been clearly defined. Some single center series suggest benefit of adjuvant radiotherapy in conjunction with systemic chemotherapy in the setting of locally advanced and regionally metastatic disease, while others fail to support such an approach. In addition, palliative radiotherapy may be considered in patients with symptomatic (e.g. bleeding) or locally-advanced disease who are unfit for surgery.

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10. Abbreviations

Upper tract urothelial carcinoma (UTUC).
Urothelial carcinoma (UC)
Computed tomographic urography (CTU)
Intravenous pyelography (IVP)
Magnetic resonance urography (MRU)
Fluorescence in situ hybridization (FISH)
Bacille Calmette Guerin (BCG)
Gemcitabine plus cis-platinum (GC)
Methotrexate, vinblastine, Adriamycin, and cis-platin (MVAC)
Radical nephroureterectomy (RNU)

Videos

Thulium Laser Ablation

Retroperitoneal Lymph Node Dissection: Learning Module for Trainees

Robotic Xi Right Nephroureterectomy with Bladder Cuff Excision

Robotic Nephroureterectomy for Upper Tract TCC

Robotic Distal Ureterectomy and Boari flap Ureteroneocystostomy after aorto-bifemoral bypass

Introduction of supine extraperitoneal laparoscopic nephroureterectomy without patient repositioning

Presentations

Upper Tract Neoplasms Presentation

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