Upper tract neoplasms

Herzog

Background

- Upper tract tumors include benign and malignant tumors of the ureter and renal collecting system (pelvis, infundibula, and calyces)
- 90% of upper tract malignancies are of urothelial origin (UTUC)
  - squamous cell carcinoma, adenocarcinoma, and small cell cancer are much less common
- **Benign** tumors of the upper tract include fibroepithelial polyps, inverted papillomas, fibromas, cystic ureteritis, and von Brunn's nests
- Tobacco is the primary dose-dependent risk factor, accounting for 25–60% of UTUC

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Background

- UTUC comprises only 5-10% of all urothelial cancers
  - majority of urothelial cancers arise from the bladder
- UTUC tends to present with higher stage disease(60-65%) compared to bladder cancer
- 2:1 male to female ratio (4:1 in bladder cancer)
- Stage for stage, outcomes similar for renal pelvis versus ureteral UTUC

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Risk Factors

Smoking
Bladder cancer (CIS, multifocality, proximity to ureteral orifice)
Lynch syndrome
Aristolochic acid (Balkan nephropathy, Chinese and Taiwanese herbal nephropathy)
Arsenic
Analgesics
Occupational exposure (petroleum, plastic, coal, tar, dyes)
Chronic inflammation and infection
Cyclophosphamide

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Risk factor

- Aristolochic acid is a mutagen found in *Aristolochia clematitis* and related plants
  - used in Eastern Asian (China, Taiwan, Vietnam, India) herbal remedies
  - Aristolochic acid toxin causes nephropathy as well as UTUC
- Causative factor in Balkan nephropathy as well as Chinese and Taiwanese herbal nephropathy

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Bladder Cancer as a Risk Factor for UTUC

- Risk for UTUC in patients with prior bladder cancer ranges from 0.8-7%
- Patient with low-risk bladder cancers (low grade, non-invasive) and longer expected survival may be at higher risk for UTUC given prolonged risk period and follow-up
- Multifocal bladder cancer and CIS associated with higher risk of UTUC
- Double J ureteral stenting during TURBT has also been suggested as a potential risk factor for future upper tract recurrence

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Bladder Cancer as a Risk Factor for UTUC

- 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
- 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

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Lynch syndrome

- Approximately 3-28% of Lynch syndrome patients develop UTUC
- Lynch syndrome is associated with colon, small bowel, endometrial, and ovarian malignancies
- No established guidelines to screen Lynch patients for UTUC
  - **NCCN suggest annual urinalyses starting at age 30-35**
  - **Routine use of urine cytology is not recommended due to low sensitivity and specificity.**
  - No formal recommendation for routine upper tract imaging
- Many of these patients already undergo imaging for follow-up of a treated Lynch syndrome-associated malignancy

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Lynch syndrome

- 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.
- 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
- Lynch syndrome states “consider tumor screening for mismatch repair (MMR) deficiency in urothelial carcinomas regardless of age

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Lynch syndrome

- 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.

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Symptoms and evaluation

- Patients with UTUC are often asymptomatic
- Presenting complaints include asymptomatic microhematuria, gross hematuria, flank pain
- Mainstay of diagnosis is endoscopic evaluation and biopsy
- Percutaneous biopsy limited to larger or infiltrative tumors

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Initial Evaluation

- Labatory evaluation should include a BMP, LFTS, UA with micro, urine culture, and cytology
  - A positive cytology with negative cystoscopy / blue light cystoscopy raises the possibility of prostatic UC or UTUC
  - No firmly established screening role for other urinary biomarkers
- Cross sectional imaging
  - CT urogram
  - MR urogram for patients with severe iodinated contrast allergy, or inadequate renal function
  - CT chest should be obtained in patients with high-risk disease
- Renogram (Mag3, DMSA) can be obtained for differential function for surgical planning purposes

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Operative Evaluation

- Cystoscopy, retrograde pyelogram, and ureteroscopic evaluation

- 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.

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Operative Evaluation

- When possible, biopsies and selective cytologies should be achieved
  - Access sheath can facilitate biopsies
  - Ureteroscopic biopsy using biopsy forceps (Pirhana® forceps), backloaded BIGopsy® forceps can sample tissue for grade and histology
  - Alternative biopsy options include basketing (flat wire and Nitinol) and brush biopsies
- Selective washings *in addition* to biopsy can serve as an additional prognosticator
- In the absence of a solid tumor, a positive selective cytology suggests the presence of CIS

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Staging

- Accurate grading and staging of UTUC is challenging
  - limited by the size of endoscopic biopsy equipment available
- Cross sectional imaging does not accurately stage invasive disease
- High frequency endoluminal ultrasound and confocal laser endomicroscopy remain experimental modalities for upper tract staging

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NCCN staging

T	**Primary Tumor**
TX	Primary tumor cannot be assessed
T0	No evidence of primary tumor
Ta	Papillary noninvasive carcinoma
Tis	Carcinoma *in situ*
T1	Tumor invades subepithelial connective tissue
T2	Tumor invades the muscularis
T3	For renal pelvis only: Tumor invades beyond muscularis into peripelvic fat or the renal parenchyma. For ureter only: Tumor invades beyond muscularis into periureteric fat
T4	Tumor invades adjacent organs, or through the kidney into the perinephric fat.

N	**Regional Lymph Nodes**
NX	Regional lymph nodes cannot be assessed
N0	No regional lymph node metastasis
N1	Metastasis ≤2 cm in greatest dimension, in a single lymph node
N2	Metastasis >2 cm in a single lymph node; or multiple lymph nodes

M	**Distant Metastasis**
M0	No distant metastasis
M1	Distant metastasis

Histologic Grade (G)
For urothelial histologies, a low- and high-grade designation is used to match the current WHO/ISUP recommended grading system:

LG	Low-grade
HG	High-grade

For squamous cell carcinoma and adenocarcinoma, the following grading schema is recommended.

GX	Grade cannot be assessed
G1	Well differentiated
G2	Moderately differentiated
G3	Poorly differentiated

***Table 4.* AJCC Prognostic Groups**

	T	N	M
Stage 0a	Ta	N0	M0
Stage 0is	Tis	N0	M0
Stage I	T1	N0	M0
Stage II	T2	N0	M0
Stage III	T3	N0	M0
Stage IV	T4	NX, N0	M0
	Any T	N1	M0
	Any T	N2	M0
	Any T	Any N	M1

Risk Stratification

Important for helping guide treatment decisions

- Low risk disease may be more amenable to organ preservation
- **If any high-risk variables are present, then the patient is considered high-risk**

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

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Treatment Options

- Organ sparing approaches may decrease risk of CKD
  - Endoscopic: ureteroscopic laser ablation, percutaneous resection
  - Segmental resection
  - Intracavitary mitomycin C (Jelmyto™)

- Radical nephroureterectomy with/without regional lymphadenectomy
  - Open
  - Laparoscopic
  - Robotic

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Endoscopic Management

- Preferred in low volume, low grade disease
- Tumors should be accessible via flexible ureteroscopy with the goal of complete ablation/removal
  - Laser ablation and monopolar fulguration are both options for ablation
  - Larger tumors of the collecting system can be approached percutaneously
- Compared to radical nephroureterectomy, endoscopic management of low-grade disease confers increased risk for local recurrence, though not associated with higher risk for death or metastases

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Intracavitary Treatment

Intraluminal therapy for UTUC remains challenging

- Delivery routes
  - antegrade via percutaneous nephrostomy tube
  - retrograde via a ureteral catheter
  - retrograde via "passive reflux" with an indwelling ureteral stent
    - 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

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Intracavitary Treatment- BCG

- *Most commonly used in intermediate and high risk bladder cancer after complete TURBT*
  - Mechanisms of action involve both the innate and adaptive immune system activation, as well as direct cytotoxic effect on tumor cells.
  - Efficacy for treating CIS (40% recurrence, 5% progression) in the upper urinary tract may be similar to the response rates observed for bladder cancer
  - The efficacy for treatment of Ta/T1 lesions is lower (59% recurrence, progression 41%)
- At this time, intraluminal BCG is not recommended for routine management of UTUC

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Upper Tract Mitomycin (Jelmyto™)

- 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.
- FDA approved for patient with low volume (< 1.5cm), biopsy proven low grade cancer based on results of OLYMPUS trial

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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.

- 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.

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OLYMPUS TRIAL

- 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%).

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Upper Tract Mitomycin (Jelmyto™)

- Can be used for chemo-ablation of residual tumor in the collecting system
- 59% complete response at 3 months; 70% of those who responded and completed 12-month follow-up had continued complete response
- Adverse events common, including 44% risk of ureteral stenosis
- 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. Possibly prevents ureteral stenosis

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Upper Tract Mitomycin (Jelmyto™)

- Instilled once weekly for 6 weeks, followed by monthly maintenance through one year
- Usually instilled retrograde by ureteral catheter (via cystoscopy with fluoroscopy in clinic)
- Initial attempts at antegrade instillation via a percutaneous nephrostomy tube have been published with good success (albeit in a small sample size)
- Potential benefits of antegrade instillation:
  - Ease of instillation
  - Possible decreased ureteral stenosis rates

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Segmental Ureterectomy

- Best suited for small, focal tumors not amenable to ureteroscopic management
- Distal ureteral tumors may be managed with distal ureterectomy, formal bladder cuff excision, and reimplant
  - Adjunctive maneuvers to allow tension-free reimplant include Psoas hitch, Boari flap, contralateral bladder mobilization, nephropexy
- More proximal ureteral tumors can be managed by segmental ureterectomy and primary ureteroureterostomy or ureterocalicostomy in appropriate kidneys and with adequate ureteral mobilization
- Regional lymphadenectomy should be considered for prognostic and possibly therapeutic purposes

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Segmental Ureterectomy

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

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Radical Nephroureterectomy (RNU)

Remains the most definitive option for treatment for high risk UTUC

- Involves complete removal of the kidney with surrounding Gerota's fascia, entire ureter, and a bladder cuff
- Can be approached laparoscopically, robotically, or open
- The ureter is traditionally clipped early to prevent disrupted tumor from spilling into the bladder
- The adrenal gland is not routinely resected unless there is concern for direct involvement
- **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**

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Radical Nephroureterectomy (RNU)

- The ureter is traditionally clipped early to prevent disrupted tumor from spilling into the bladder
  - Bladder cuff surrounding the ipsilateral ureteral orifice can be resected extravesically, transvesically, or endoscopically
- Following RNU and bladder closure, intravesical chemotherapy (e.g. mitomycin-C, gemcitabine, pirarubicin) is associated with a decreased risk of intravesical recurrence
  - This can be administered as a single dose at time of nephroureterectomy or at time of voiding trial

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Preventing Intravesical Recurrences

- Risk for bladder cancer recurrence after upper tract cancer is high, 5-40%
  - Patients require close cystoscopic surveillance
- Two randomized prospective studies have shown a significant reduction in bladder cancer recurrence after nephroureterectomy using intravesical therapy
- Intravesical instillation of an approved chemotherapeutic agent (such as mitomycin-C or gemcitabine) after nephroureterectomy should be considered prior to catheter removal

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Lymph Node Dissection

Lymphadenectomy **at the time of RNU** has been investigated in several retrospective studies and might benefit patients with high-risk disease for staging

- **Template-based lymph node dissection should be considered as an adjunct to nephroureterectomy and distal ureterectomy in patients with high grade UTUC**
- The number of lymph nodes removed has achieved independent predictor status for cancer-specific mortality and overall survival in retrospective studies
- Retrospective data suggest that at least eight lymph nodes should be removed to ensure a true likelihood of having pN0 status.

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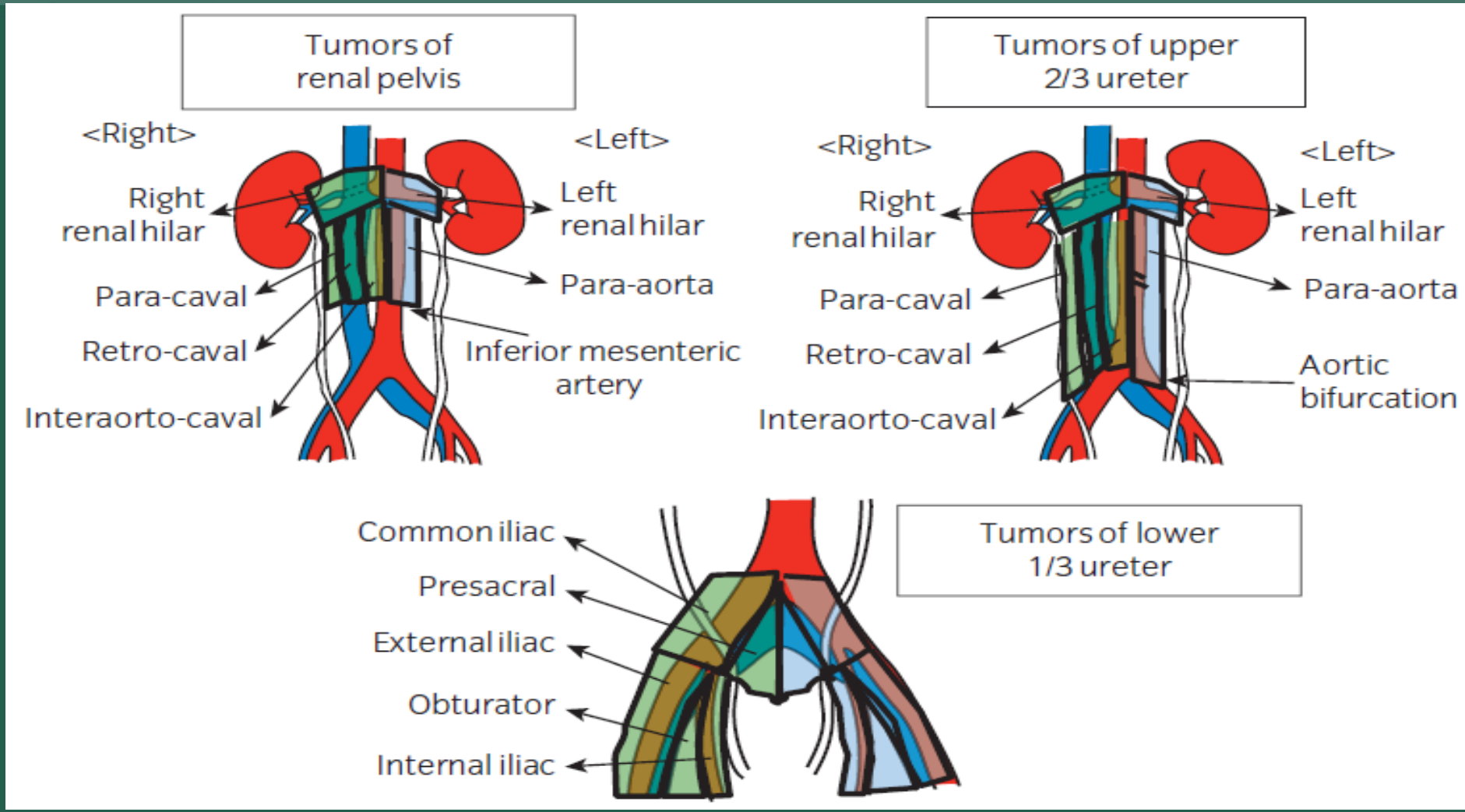
Landing Sites for UTUC



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Neoadjuvant Chemotherapy

- Neoadjuvant chemotherapy is presumed to play an important role in invasive UTUC based on muscle-invasive bladder cancer clinical trials
- **Majority of patients develop CKD and are therefore ineligible for cisplatin therapy after surgery**
  - Presurgical therapy capitalizes on a patient's maximal renal function for optimal multimodality therapy
- Since staging of UTUC is difficult, concerns exist about potential overtreatment

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Neoadjuvant Chemotherapy

- Retrospective data: NAC is associated with ~15% rate of pT0 disease and significant down-staging at time of RNU
- Cisplatin-based multi-agent chemotherapy regimens, such as Gemcitabine plus cisplatin (GC) or methotrexate, vinblastine, Adriamycin, and cisplatin (MVAC) are preferred
- Prospective intergroup study of neoadjuvant dose dense MVAC prior to nephroureterectomy in patients with high grade UTUC (ECOG-ACRIN 8141)
  - Complete pathologic response rate of 14% and a 62% rate of < pT2 disease.
- Role of immunotherapy as neoadjuvant therapy in patients with UTUC is being evaluated

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Adjuvant Chemotherapy

- Randomized 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 disease-free and overall survival at median follow-up 48 months (HR 0.51 and 0.52)
- Adjuvant chemotherapy was associated with a 30% reduction in risk of death but did not meet clinical significance ($p = 0.09$) at follow-up
- Given difficulties in staging UTUC (pre-operatively), adjuvant chemotherapy after nephroureterectomy may more appropriately select patients for additional chemotherapy and minimize overtreatment.

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Adjuvant Chemotherapy

CheckMate 274 study **evaluated adjuvant nivolumab** 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.. 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.
- 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.

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Adjuvant 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.

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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

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%)

Treatment of Metastatic UTUC

- 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.

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Treatment of Metastatic UTUC

- 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
- .

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Treatment of Metastatic UTUC

- 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: 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.
- The most common irAEs include colitis, endocrinopathies, nephritis, liver toxicity, skin rash or pruritis, and pneumonitis, but can include many others.
- Treatment includes early diagnosis and cessation of therapy with steroid treatment in severe cases.

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Radiaton 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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