

Upper Tract Nephron Sparing Urothelial Cancer Treatment

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Disclosures

- Boston Scientific
 - Data Safety Monitoring Committee Member
- NCCN
 - Chair, Early Detection for Prostate Cancer Guidelines Panel

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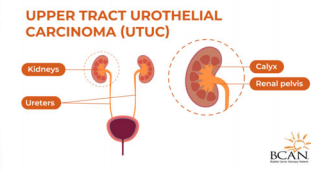
Agenda

- Epidemiology and Staging of Upper Tract Urothelial Carcinoma
- Treatment Options for Nephron Sparing Approach
 - Endoscopic Management
 - Topical Chemotherapy
 - Surgical Options
- Surveillance

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Upper Tract Urothelial Carcinoma (UTUC)

- Rare malignancy
 - Approximately 7000 cases per year
 - 5% of urothelial cancers
 - 10% of renal tumors
- 2-3x more commonly diagnosed in men
- 80-90% in white patients
 - Decreasing incidence among white patients
 - Increasing in Black patients, with 30% higher mortality
- Urothelial carcinoma of bladder following treatment of UTUC is approximately 15% to 50%




UPPER TRACT UROTHELIAL CARCINOMA (UTUC)

Kidneys, Ureters, Calyces, Renal pelvis

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Petros, Transl Androl Urol 2020

Risk Factors

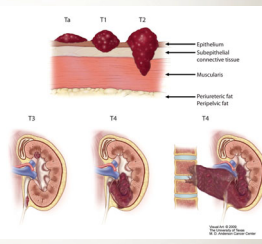
- Bladder cancer
 - CIS raises risk of UTUC by 2-4x
- Smoking (2-7x)
- Aristolochic acid
- Lynch Syndrome
- Arsenic
- Alcohol abuse



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UTUC Presentation and Staging

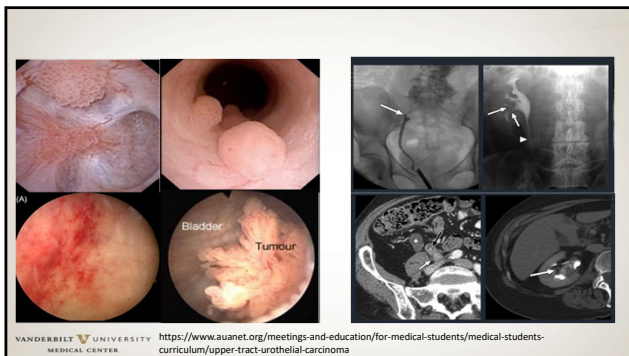
- 2/3rd present with gross or microscopic hematuria
- 25% present with flank pain due to obstruction
- Hydronephrosis (37-80%) indicates more advanced disease
 - Consider neoadjuvant chemotherapy
- UA/UCx, Cytology, Hgb, Cr, CTU/MRU, Cystoscopy, URS → biopsy/laser
- 40-50% of patients have non-muscle invasive UTUC (pTa/T1)
 - 10-25% of patients presents with metastasis at diagnosis



Ta, T1, T2, Epithelium, Subepithelial connective tissue, Muscularis, Perivesicular fat, Peripelvic fat

T3, T4

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Petros, Transl Androl Urol 2020
Vikram et al, Am J Roentg 2009



EAU and AUA Risk Stratification

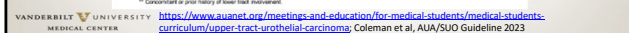
Table 5: Presurgical Clinical Risk Categories

| Features | Risk Stratification | | | |
|----------------------------------|---------------------|-----------------|-------------------------|-------------------------|
| | Low-risk | | High-risk | |
| Biopsy Grade | Low-Grade | High-Grade | Low-Grade | High-Grade |
| Sub-institution | Favorable | Unfavorable | Favorable | Unfavorable |
| Cytology* | Negative cytology | No HGUC | Any Cytology | HGUC |
| Radiology* | No invasion | No invasion | Invasion | Invasion |
| | No obstruction | Obstruction | No obstruction | Obstruction |
| Appearance | Normal nodes | Normal nodes | Normal nodes | Suspicious nodes |
| | Unifocal | Multifocal | Unifocal | Multifocal |
| | Papillary | Papillary | Papillary | Solid or flat |
| Lower Tract Involvement** | No involvement | Involvement | No involvement | Involvement |
| Adjuvant Treatments | Therapy | | | |
| Systemic Therapy | Preferred | May be offered | Rare, selected cases | Pullulation |
| | 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: non-specific, negative for HG urothelial carcinoma (NHGUC), atypical urothelial cells (AUC), suspicious for HG urothelial carcinoma (SHGUC), HG urothelial carcinoma (HGUC), LG urothelial carcinoma (LGUC), and other malignancies.

** Concurrent or prior history of lower tract involvement.

<https://www.auanet.org/meetings-and-education/for-medical-students/medical-students-curriculum/upper-tract-urothelial-carcinoma> Coleman et al, AUA/SUO Guideline 2023



Rationale for Nephron Sparing Approach

- Approximately 40-50% of patients have non-invasive disease
- Median age at presentation is >70y
- Risk factors for surgery
 - Comorbidity
 - Renal insufficiency/CKD
 - Solitary kidney
 - Bilateral disease
 - Ureter only disease



Factors Complicating Nephron Sparing

Disease factors:

- Aggressive
- Multifocal
- Recurrence Rates

Surgical factors:

- Approach
- Instruments
- Scopes, Visualization
- Adequate Specimen

ENDOSCOPIC MANAGEMENT CONSIDERATIONS

How Do We Improve Our Chances Endoscopically?

- 1)Surgical approach
- 2)Instrumentation
- 3) Scope selection



Preoperatively

- Appropriately selected
- Appropriately staged
- Counseled—staged procedures

| | |
|-----------------------------------------------------------------------------------------|--------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| <p>Retrograde ureteroscopy Best for low volume ureteral and renal tumors</p> | <p>Antegrade approaches Larger volume renal tumors and proximal ureteral tumors</p> <p>Retrograde not possible Lower pole calyx Urinary diversion</p> |
|-----------------------------------------------------------------------------------------|--------------------------------------------------------------------------------------------------------------------------------------------------------------------------|

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Goals of Either Surgical Approach

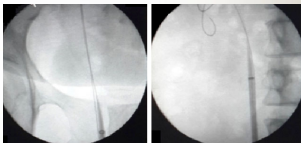
- Find tumor(s)
 - Cystoscopy
 - Contralateral kidney
- Obtain tissue/washings
- Systematically ablate tumor(s)
- Minimize trauma



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Retrograde Access

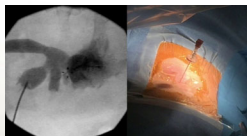
- Clear ureter first
- Access Sheath
 - Improve ease of access/biopsies
 - Lower intra-renal pressures
 - Improves visibility
 - Flexibility w/ instrumentation
- Ureteral tumor: safety wire



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Antegrade Approach

- Main advantage is can use larger instruments
 - Better grading/staging?
 - Nephrostomy can be used for 2nd look, adjuvant topical therapy
- Percutaneous access
 - Bleeding/infection risk higher, risk of tumor seeding



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Treatment utilization and overall survival in patients receiving radical nephroureterectomy versus endoscopic management for upper tract urothelial carcinoma: evaluation of updated treatment guidelines

- 16,783 patients with <=cT1 UTUC from 2004-12 in NCDB
 - 851 with low-risk disease (<2cm, LG, Stage I or less)
- Examined OS with Endoscopic Treatment (ET) vs Radical Nephroureterectomy (NU)
- Compared outcomes for <1cm vs <2cm based on change in EAU guidelines

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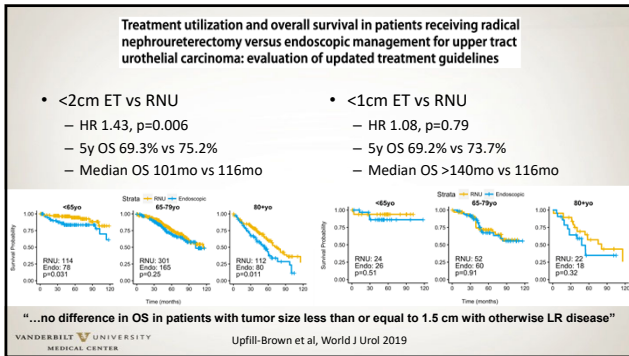
Upfill-Brown et al, World J Urol 2019

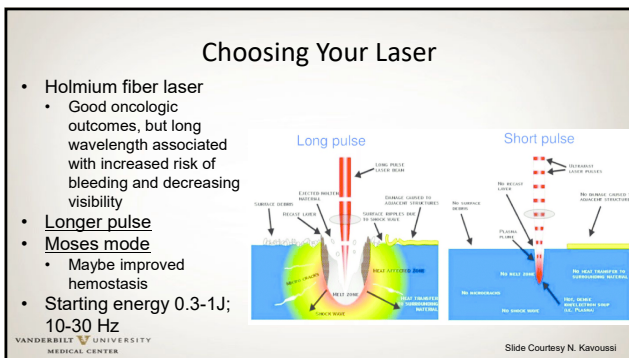
Treatment utilization and overall survival in patients receiving radical nephroureterectomy versus endoscopic management for upper tract urothelial carcinoma: evaluation of updated treatment guidelines

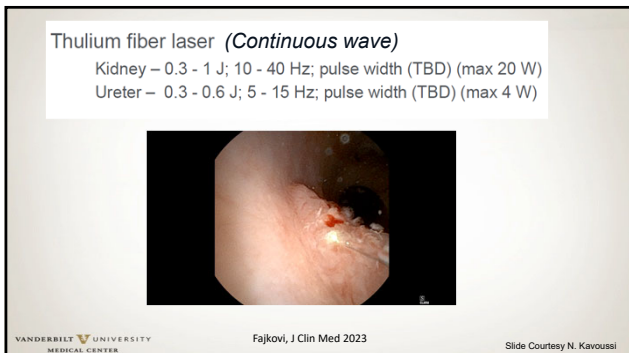
- Factors associated with ET vs RNU
 - Ureteral location -Healthier
 - LG -Higher income
 - Size and stage -Treatment at academic facility
 - Male -More recent year of treatment
 - Older age
- For 851 patients with LR disease under 2017 guidelines (<2cm)
 - 323 (38%) received ET and 527 (62%) received RNU
- For 202 patients with LR disease under 2015 guidelines (<1cm)
 - 104 (51%) who received ET, and 98 (49%) received RNU

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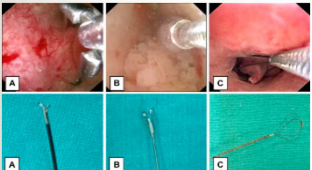
Upfill-Brown et al, World J Urol 2019







Biopsy Forceps Pros and Cons



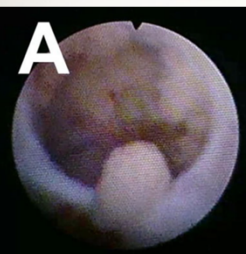
A) Piranha forceps (3f)
 -flat tumors
 -worse bx yield (crush artifact)

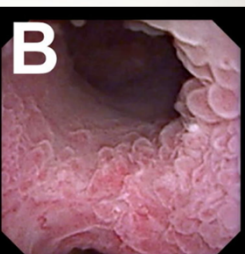
B) BigOpsy (6f)– tip 4mm³
 -renal pelvis vs upper pole; need access sheath
 -good bx yield
 -difficulty w flexion and visualization

C) Baskets (1.5-3f)
 -papillary
 -good bx yield
 -difficult w flat tumors

Breda et al, World J Urol 2019
 Lama et al, Urology 2018
 Slide Courtesy N. Kavoussi

Choosing Your Scope: Fiberoptic vs Digital

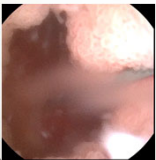
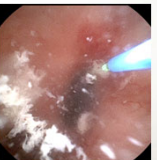




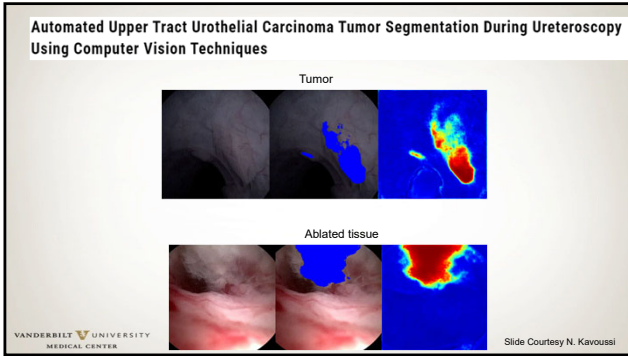
Slide Courtesy N. Kavoussi

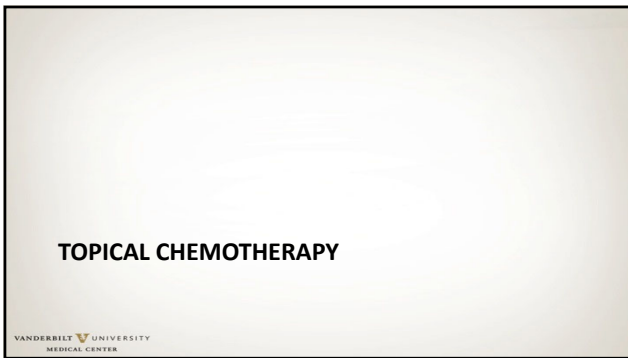
Challenges—Visualization!

- Depth of field: 6mm
- Field of view: 10mm
- Hemorrhage and debris
- 50% of patients require staged procedure

Sanguedolce, J Endourol 2021
 Slide Courtesy N. Kavoussi





Non-Muscle Invasive Bladder Cancer Sets the Paradigm

- BCG
- Mitomycin C
- Valrubicin
- Gemcitabine
- Epirubicin
- Docetaxel
- Nadofarogene firadenovec-vnvc
- Nogapendekin alfa inbakicept
- TAR-200/Cetrelimab

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Upper Tract Topical Therapy

- Typically delivered antegrade via 10F nephrostomy tube
 - Can be given retrograde via 5F ureteral catheter or stent
 - Retrograde instillation with open-ended catheter produced the greatest staining with 83.5% of total area stained in ex vivo porcine model
- Most common include BCG +/- IFN, mitomycin C, pirarubicin, epirubicin, gemcitabine, and Adriamycin
 - Up to 40% recurrence
- Mitomycin C as induction and adjuvant therapy for <T2 UTUC, demonstrated 3y RFS 60%, PFS 80%, and RNU-free survival 76%
- 70–80% of patients with low-grade and low- stage UTUC undergo RNU

VANDERBILT UNIVERSITY MEDICAL CENTER Pollard et al, Urology 2013; Metcalfe et al, J Endourol 2017; Chien et al, Front Urol 2022; Upfill-Brown et al, World J Urol 2019

Intraluminal Mitomycin C (Jelmyto)

- Reverse thermal hydrogel, that is instilled as a chilled liquid and either instilled antegrade via PCN or retrograde via ureteral catheter
- Fills and conforms to the pelvis, then after 4-6 hours is slowly excreted
- Side effects/AEs
 - Ureteral narrowing
 - UTI
 - Hematuria
 - N/V
 - Pain
- Mechanism of tumor cell destruction by DNA alkylation and the consequent inhibition of DNA synthesis



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Primary chemoablation of low-grade upper tract urothelial carcinoma using UGN-101, a mitomycin-containing reverse thermal gel (OLYMPUS): an open-label, single-arm, phase 3 trial

- 71 patients in single-arm, Phase III, open label trial
 - 61 completed 6 treatments
- Primary or recurrent biopsy-proven, low-grade UTUC
 - Up to 1.5cm
- Receive six instillations of once-weekly UGN-101
- Primary outcome- CR
 - Negative 3mo URS
 - Negative cytology
 - Negative biopsy
- Most treatments were administered using a 7F ureteral catheter

VANDERBILT UNIVERSITY MEDICAL CENTER Kleinmann et al, Lancet Oncol 2020

Primary chemoablation of low-grade upper tract urothelial carcinoma using UGN-101, a mitomycin-containing reverse thermal gel (OLYMPUS): an open-label, single-arm, phase 3 trial

- 59% with CR
 - 11% PR
- Estimated 12mo durability of response- 84.2%
- Median time to recurrence- 13mo
- 37% with at least one SAE
 - Ureteric stenosis (7%)
 - 2 eventually needed RNU (yp0)
 - Hydronephrosis (6%)
 - Flank pain/colic (4%)

| All treated patients (n=71) | |
|-----------------------------|----------|
| Complete response | 42 (59%) |
| No complete response | 29 (41%) |
| Partial response | 8 (11%) |
| No response | 12 (17%) |
| High-grade patient* | 6 (8%) |
| Indeterminate† | 3 (4%) |

*High-grade patients were those with the emergence of high-grade disease at primary disease evaluation that was not detected at baseline. †Indeterminate patients were those who had "undetermined" (or "not done") recorded on the case report form page "Evaluation of Response (Target Area Lesions)" at primary disease evaluation and at re-evaluation, or who had no re-evaluation. For the primary analysis these patients are deemed non-complete responders.

Table 3: Primary disease evaluation results (local pathology)

Kleinmann et al, Lancet Oncol 2020

Mitomycin Gel (UGN-101) as a Kidney-sparing Treatment for Upper Tract Urothelial Carcinoma in Patients with Imperative Indications and High-grade Disease

- 52 renal units in patients with imperative indication
 - Solitary kidney
 - CKD (GFR <30ml/min)
 - Bilateral UTUC
 - Unfit or unwilling to undergo RNU
- 12 patients with high-grade disease
- 34% had complete tumor ablation
- 17 patients (40%) were NED on URS
 - 88% maintained NED at median follow-up of 10.8 mo

Rose et al, Eur Urol Focus 2023

Mitomycin Gel (UGN-101) as a Kidney-sparing Treatment for Upper Tract Urothelial Carcinoma in Patients with Imperative Indications and High-grade Disease

Table 3 - Clinicopathologic and oncologic outcomes for patients treated with UGN-101 for high-grade upper tract urothelial carcinoma

| Patient | CID | Tumor stage | Tumor location | CA before UGN-101 | Disease at PDE | DR | TTR (mo) | DP | TSAP | TTP (mo) |
|---------|-----|-------------|----------------|-------------------|----------------|----|----------|----|---------|----------|
| 1 | ✓ | T1 | RP | ✓ | NED | – | – | – | – | – |
| 2 | ✓ | T1 | RP | ✓ | (+) | – | – | – | – | – |
| 3 | ✓ | T1 | RP+U | X | (+) | – | – | – | – | – |
| 4 | ✓ | Ta | RP | X | NED | ✓ | 10.8 | ✓ | pT3N2 | 10.8 |
| 5 | ✓ | Ta | RP | ✓ | NED | – | – | – | – | – |
| 6 | ✓ | Ta | RP+U | ✓ | NED | ✓ | 5.9 | – | – | – |
| 7 | ✓ | Ta | RP | ✓ | NED | – | – | – | – | – |
| 8 | ✓ | Ta | RP | ✓ | (+) | – | – | – | – | – |
| 9 | ✓ | Ta | RP | ✓ | (+) | – | – | – | – | – |
| 10 | ✓ | Ta | RP | ✓ | (+) | – | – | – | – | – |
| 11 | ✓ | Ta | RP | X | (+) | – | – | ✓ | cTaN1M1 | 12.2 |
| 12 | X | Ta | RP | X | – | – | – | – | – | – |

CID = completed indication; CA = complete ablation; RP = renal pelvis; U = ureter; PDE = primary disease evaluation; NED = no evidence of disease; (+) = disease present; DR = disease recurrence; TTR = time to recurrence; DP = disease progression; TSAP = tumor status after progression; TTP = time to progression.

"UGN-101 shows efficacy as a kidney-sparing option for patients with UTUC with imperative indications. The benefits...include the ability to delay RNU and the morbidity associated with hemodialysis."

Rose et al, Eur Urol Focus 2023

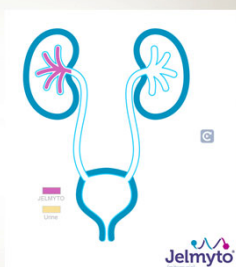
UGN-101 for UTUC

- FDA approved UGN-101 for LG UTUC in 2020
- Recommended dose 4mg/ml, total dose not exceeding 15ml

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Preparation for Antegrade Instillation

- Modify your OR template
 - Size & location of lesions → impacts optimal location of PCN placement
 - Measure renal pelvis volume & record as this determines dosing of Jelmyto
 - Alternatively, IR can measure the volume at the time of PCN placement and/or antegrade



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Slide Courtesy A. Luckenbaugh

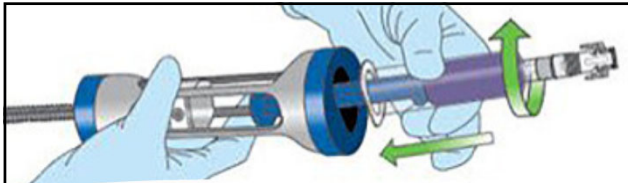
PCN Placement and Confirmation

- IR places PCN (generally 8F)
- 1 week later:
 - Antegrade nephrostogram to confirm placement
 - Urology then confirms placement in clinic
 - Flush & aspirate to confirm placement
 - Instill Jelmyto
 - Cap tube



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Slide Courtesy A. Luckenbaugh

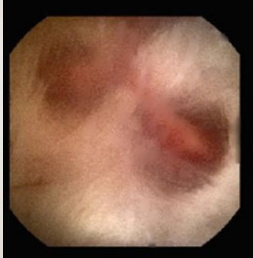


Subsequent Treatments

1. Confirm tube placement (flush & aspirate)
2. Instill Jelmyto, followed by 2cc flush
3. Cap tube
4. 6 weekly treatments

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PCN Removal



1. Antegrade nephrostogram to rule out obstruction
2. Remove PCN
3. Perform surveillance ureteroscopy 8-12 weeks after completion

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NEPHRON SPARING SURGERY

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Surgical Options

(D)
Ureteroureterostomy
34.3%
28.6%

- Distal Ureterectomy with Reimplantation +/- Psoas Hitch
- Ideally in smaller, non-invasive tumors
- Segmental Ureterectomy with UU or Ileal Transposition
- Risk of stricture
- Partial Nephrectomy/Heminephrectomy with Pyelovesicostomy or Ileal Transposition
- May need to be done *ex vivo*

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Narrative review of nephron-sparing surgical management of upper tract urothelial carcinoma: is there a role for distal ureterectomy, segmental ureterectomy, and partial nephrectomy

Table 2 Summary of studies safety, feasibility and effectiveness of robotic-assisted nephron-sparing management of ureteral tumors

| Author, year | No. of patients | HG UTUC with ≥ T2 (%) | Complications (%) | Follow-up (months) | Recurrences (%) |
|------------------------------|-----------------|-----------------------|-------------------|--------------------|-----------------|
| Saini et al., 2023, (16) | 17 | 29.4 | 23.5 | 41 | 23.5 |
| Palagonia et al., 2021, (17) | 11 | 27.3 | 36.4 | 25.5 | 36.4 |
| Campi et al., 2019, (18) | 15 | NR | 53.3 | 21 | 46.7 |
| Pugh et al., 2015, (19) | 4 | 50 | 25.0 | 21 | NR |
| Fifer et al., 2014, (20) | 10 | NR | NR | 6 | NR |
| Elsamma et al., 2014, (21) | 6 | NR | NR | 16 | NR |
| McClain et al., 2012, (15) | 6 | 16.7 | 0.0 | 33 | 16.7 |
| Singh et al., 2009, (14) | 2 | 0.0 | 0.0 | 2.5 | NR |

[†], multicenter study; HG, high grade; UTUC, upper tract urothelial carcinoma; NR, not reported.

Saini et al, Transl Androl Urol 2024

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Surgical Options: Suggestions for Approach

- Many can be performed via minimally invasive approach
- Regional lymph node dissection should be performed
- Follow oncologic principles
- Stringent surveillance needed for risk of recurrence and complications

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Strict Surveillance

- 1) Repeat tx at 6 weeks after index surgery: until tumor is gone!
- 2) Endoscopy every 3mo for first 2 years
- 3) 6mo if neg at two years
- 4) Annually after 5 years.



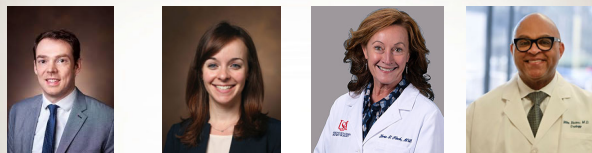
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Summary

- UTUC is a rare and aggressive cancer that requires a nuanced approach for each patient
- Nephron sparing approaches should be performed in patients with low risk disease
 - <2cm (ideally <1.5cm)
 - Low grade
 - Unifocal
 - Non-invasive
 - Accessible
- UGN-101 (Jelmyto) is a feasible option for topical chemotherapy in low grade UTUC
- Optimal visualization is needed- pick the right scope
- Surgery may be an option, but strict vigilance is necessary

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Acknowledgements



Nick Kavoussi, MD Amy Luckenbaugh, MD Lori Fleck, MD Mike Bivins, MD

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Sweet Home Alabama



Indian Springs School



Sixth Avenue Baptist Church



UAB

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Thank You!

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for
SESAUA President



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