Ology Medical Education

In my clinic: novel developments and best practices for UTUC

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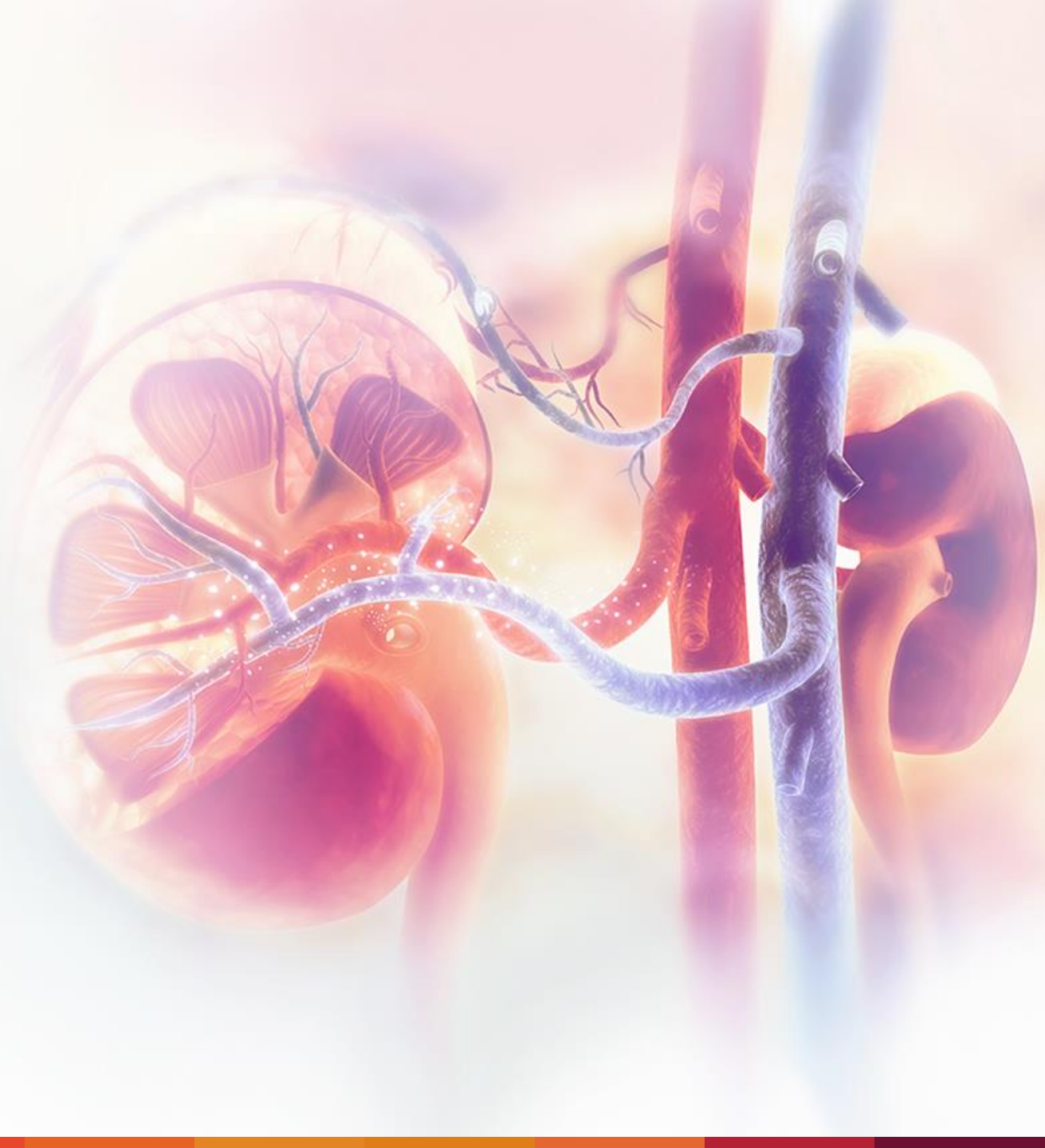

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Unmet needs in UTUC

Epidemiology

- 4,600–7,800 new cases in 2018
- Mean age: 73 years
- 3:1 men:women
- 3% bilateral UTUC, 17% concurrent with bladder cancer
- New UTUC in patients:
  - 2–4% have had prior bladder cancer
  - **20–25% have had prior CIS of the bladder** (at 10 years)
- Incidence of new bladder cancer in patients with prior UTUC is 22–47%
- Hereditary predisposition to UTUC (HNPCC, Lynch syndrome)

Recurrence

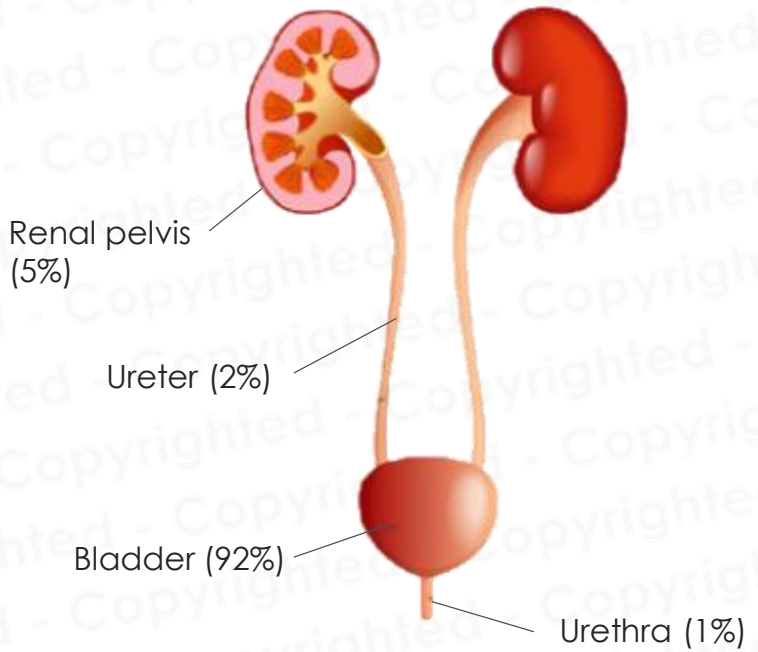
- 70–80% recurrence after surgical intervention

Standard of care

- Nephroureterectomy and bladder cuff

Survival

- 5-yr survival rates approach 90% in low-stage disease
- < 10% in cases of distant metastasis



Unmet need for more effective organ-sparing approaches in selected patients

Roberts JL, et al. Abdom Radiol (NY). 2019;44:3893-905.
Roupret M, et al. Eur Urol. 2018;73:111-22.
Concepcion RS. "Updates on Upper Tract Urothelial Cancer." August 11, 2018. Available from: https://grandroundsinurology.com/updates-on-upper-tract-urothelial-cancer/. Accessed August 2020.
Verhoest G, et al. World J Urol. 2011;29:495-501.

CIS, carcinoma in situ; HNPCC, hereditary non-polyposis colorectal cancer; UTUC, upper tract urothelial cancer; yr, year.

Risk factors for UTUC

- Tobacco
- Occupational exposures
- Balkan endemic nephropathy
- Chinese herbs
- Exposure to arsenic in drinking water
- Genetics

Hutchinson R, et al. Clin Adv Hematol Oncol. 2016;14:101-9.
Li Q, et al. Curr Urol Rep.2016;17:12.

Genetics: Lynch syndrome

- Lynch syndrome is the most common inherited cancer syndrome
  - UTUC is the third most common of the Lynch-syndrome-associated tumors (the first is colon cancer)
- Approximately 21% of UTUCs may be associated with Lynch syndrome

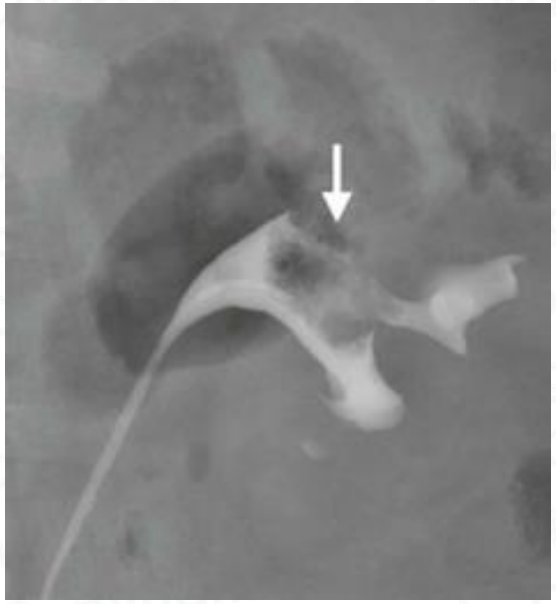
- Consider Lynch syndrome in
  - Women
  - Younger age of onset (mean age 62 years)
  - Ureteral location
  - Bilateral disease

- When should you suspect Lynch syndrome?
  - Personal or family history, tissue confirmation, and genetic evaluation

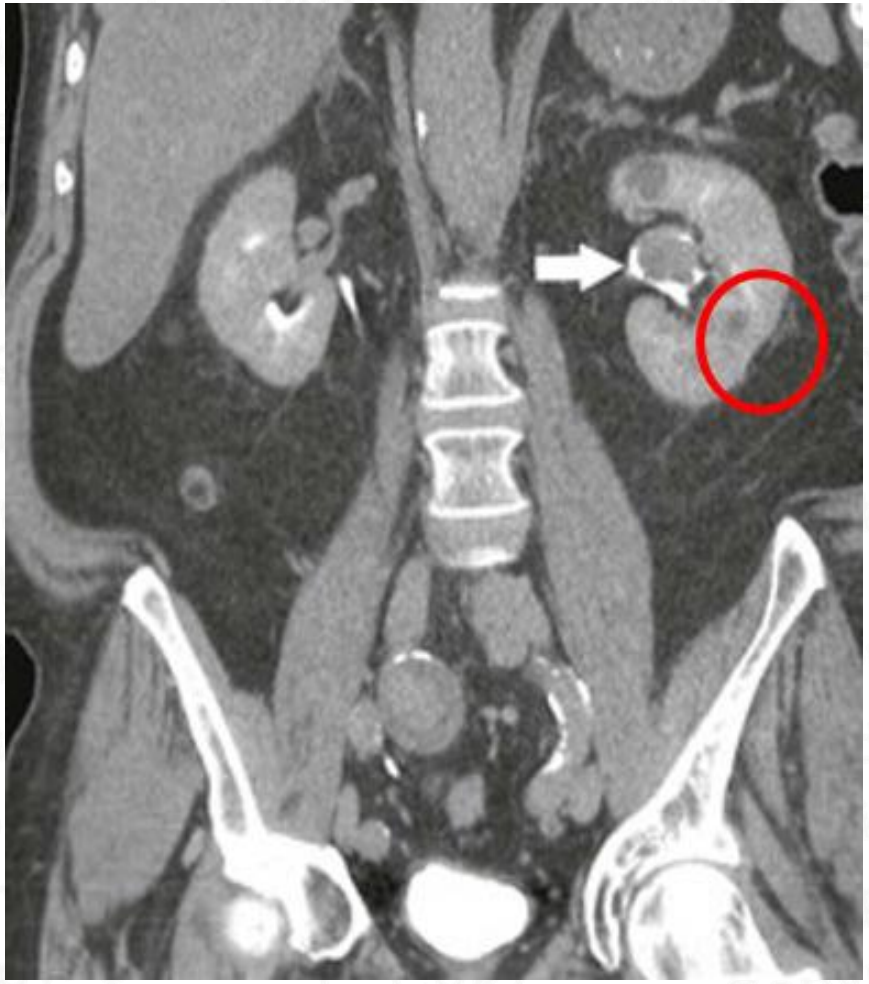
Pradere B, et al. Curr Opin Urol. 2017;27:48-55.

How do we diagnose UTUC?

- CT urogram
  - Very sensitive and specific test
- MR urogram
  - In lieu of CT urogram
    - For patients with renal impairment
- Retrograde pyelogram



Filling defect



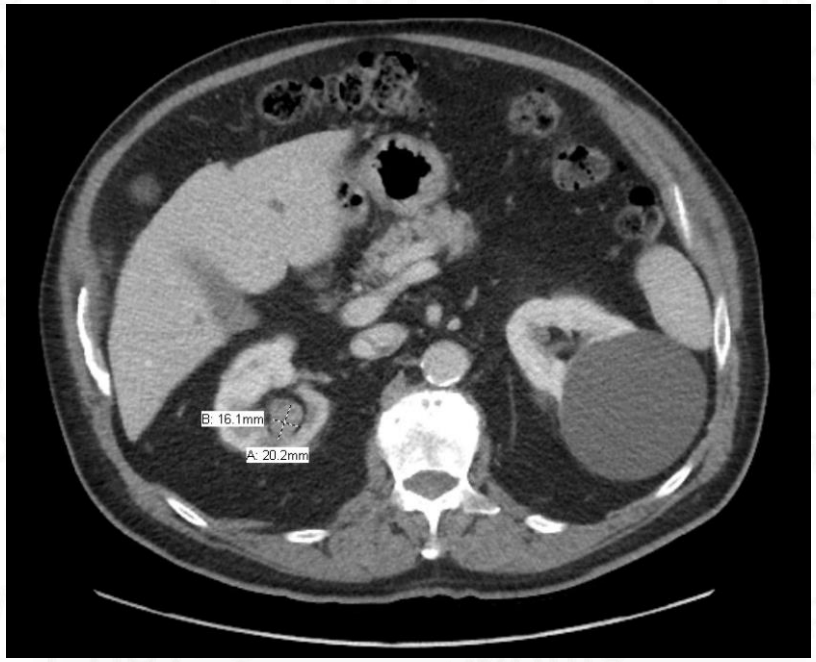
Images provided by Dr Steinberg.
CT, computed tomography; MR, magnetic resonance.

Roupret M, et al. Eur Urol. 2018;73:111-22.

Diagnostic challenges

- Biopsy
  - Ureteroscopy
  - Percutaneous biopsy
  - Cytology

- Management based primarily on grade
  - Issues with biopsy and cytology
  - Almost impossible to stage



SPECIMEN(S):
Kidney, right, biopsy

DIAGNOSIS(ES):
Right renal pelvis, biopsy:
Papillary urothelial hyperplasia.

DIAGNOSIS:

URINE, VOIDED:

- NEGATIVE FOR HIGH-GRADE UROTHELIAL CARCINOMA
- RED BLOOD CELLS

Image provided by Dr Steinberg.

Knoedler JJ, Raman JD. Ther Adv Urol. 2018;10:421-9.
Baard J, et al. Nat Rev Urol. 2017;14:181-91.

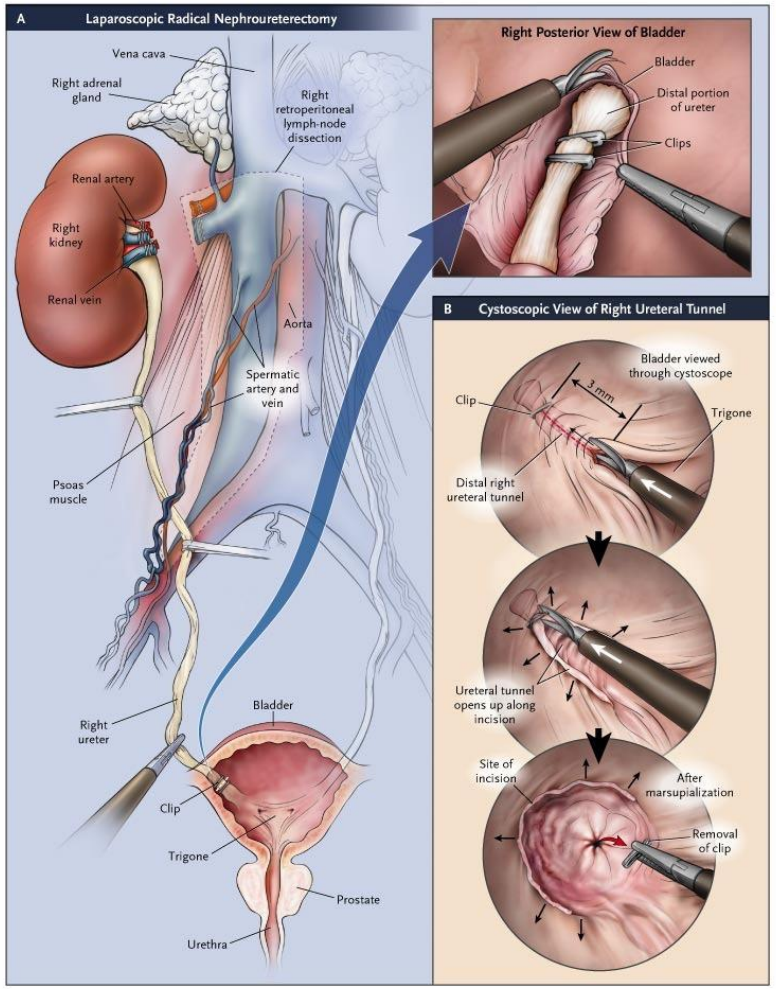
Treatment options for UTUC

- Radical nephroureterectomy (RNU)
  - Removal of the kidney and the entire ureter using a bladder cuff
- Nephron-sparing or conservative management (saving part of the entire kidney)
  - Ureteroscopic ablation
  - Intracavitary therapy
  - Removal of the segment involved with cancer
    - Segmental ureterectomy
    - Partial nephrectomy
- Systemic chemotherapy

Leow JJ, et al. OncoTargets Ther. 2020;13:1-15.

RNU in low-grade UTUC disease

- RNU is the gold standard for treatment of HG disease; its role in LG disease is unclear
  - 5-year survival in patients with LG with organ-sparing treatment is statistically similar to RNU
- RNU involves removal of renal pelvis, kidney, and entire ureter/bladder cuff with lymph node removal
- Limitations
  - Significant morbidities and complications
  - Renal insufficiency up to dialysis is a major cause of mortality
  - Risk for cardiovascular events



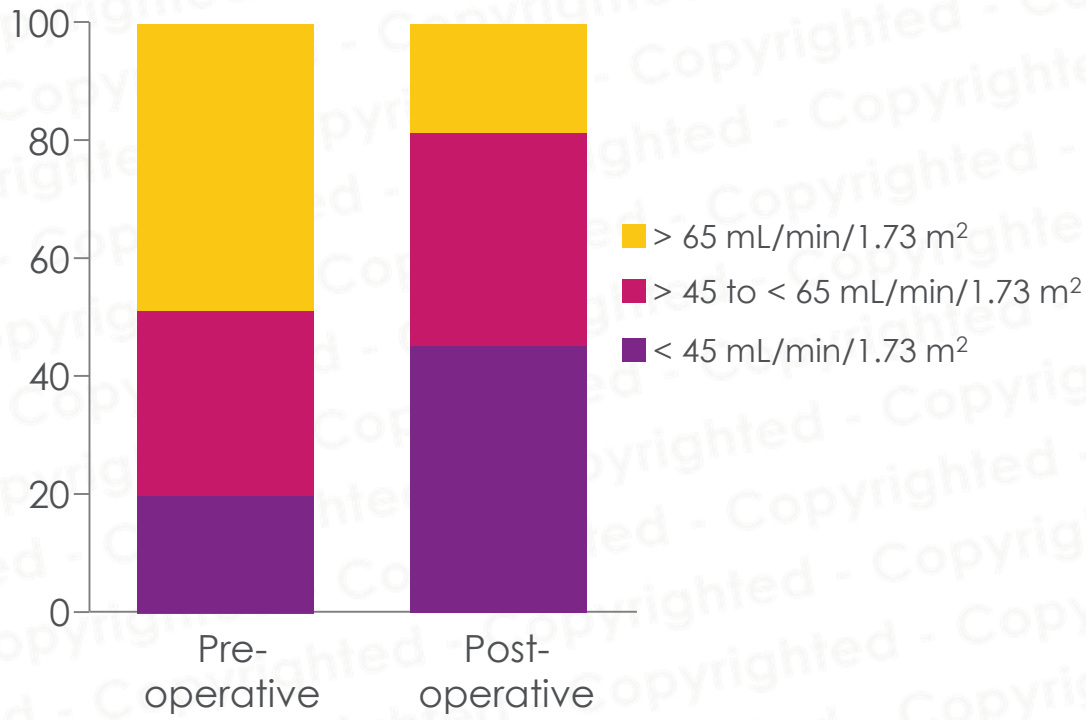
HG, high-grade; LG, low-grade.

Raman JD, et al. Urol Oncol. 2014;32:47.e9-14. Jeldres C, et al. Urology. 2010;75:315-20. Kaag MG, et al. Eur Urol. 2010;58:581-7. Dahl DM, et al. N Engl J Med. 2004;351:2102-10.

Therapeutic challenges of nephroureterectomy

- Nephroureterectomy impairs renal function
  - Overall eGFR ↓ 24%
  - eGFR (60 mL/min/1.73 m^2)
    - 49% (pre-op) → 19% (post-op)
  - eGFR (45 mL/min/1.73 m^2)
    - 80% (pre-op) → 55% (post-op)
  - Elderly patients (age > 70 years) were less likely to be eligible for perioperative chemotherapy
  - Patients with > pT3 are more likely to have decreased eGFR

Percentage of patients with pre-and post-operative eGFR in selected ranges
(4 centers, N = 388)

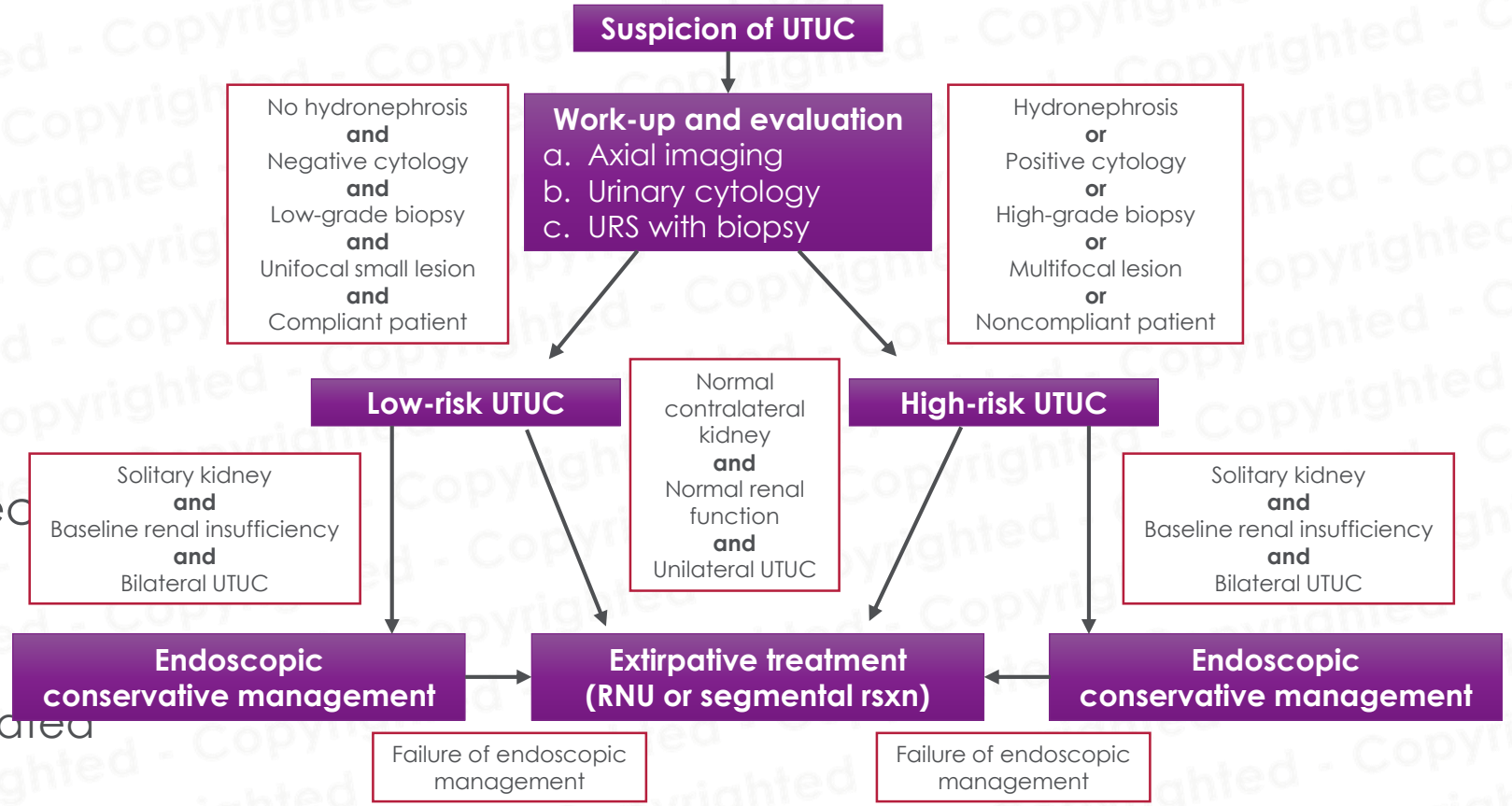


eGFR, estimated glomerular filtration rate.

Kaag MG, et al. Eur Urol. 2010;58:581-7.

Therapeutic challenges of nephron-sparing approaches

- Indications for endoscopic management
  - Low-risk disease
  - Compulsory indications
    - Bilateral lesions
    - Preexisting CKD
    - Solitary kidney
- Indications for segmental resec
  - LG or HG
  - Preserves nephrons
  - Only applicable for tumors located in the mid- or distal ureter



CKD, chronic kidney disease; rsxn, resection; URS, ureteroscopy.

Raman JD, Park R. Expert Rev Anticancer Ther. 2017;17:545-54.
Baard J, et al. Nat Rev Urol. 2017;14(3):181-91.

Therapeutic challenges of endoscopic management

Outcomes of percutaneous ablation of UTUC

Study	N	Biopsy G1/G2/G3 (LG/HG)	Follow-up (months)	UT recurrence	Progression to RNU	Outcomes
Motamedinia et al., 2016	141	73/64	66	37% LG 63% HG	13%	OS: 40%
Rastinehad et al., 2009	89	50/39	61	33%	13%	OS: 68%
Roupret et al., 2007	24	17/7	62	13%	21%	CSS: 83% OS: 79%
Palou et al., 2004	34	7/21/5	51	13%	21%	CSS: 94% OS: 74%
Suh et al., 2003	14	8/6	21	100%	36%	ND
Goel et al., 2003	20	15/5	64	65%	50%	CSS: 75%
Clark et al., 1999	17	6/7/4	24	33%	12%	CSS: 82%

Endoscopic management is associated with high recurrence and progression rates

CSS, cancer-specific survival; G, grade; ND, no data;
OS, overall survival.

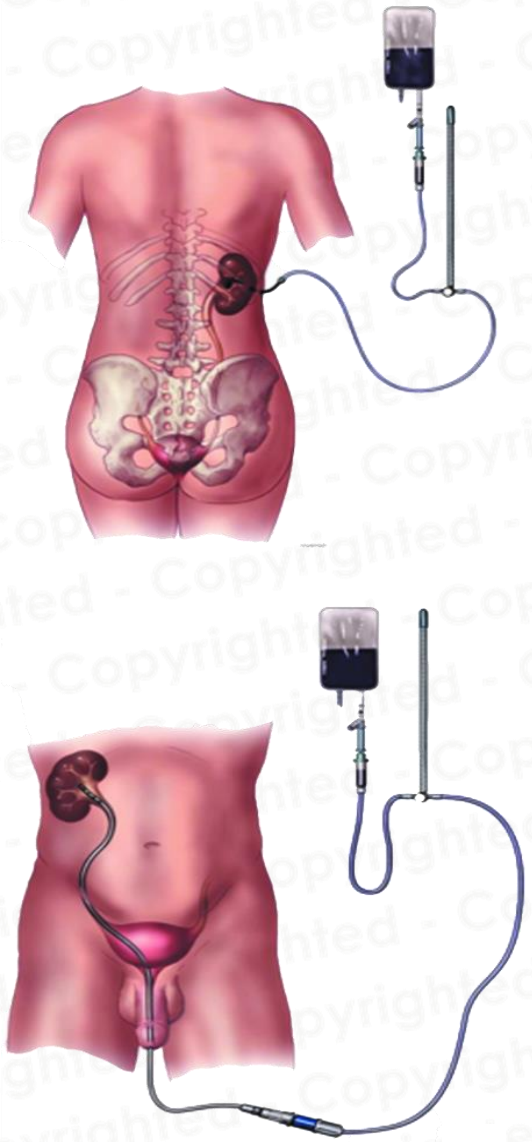
Raman JD, Park R. Expert Rev Anticancer Ther. 2017;17:545-54.

How to choose a management option?

- Location: kidney pelvis, ureter (upper, mid-, lower), one/both side(s), solitary kidney
- Size and number of tumors
- Pathology: type, HG vs LG, invasive vs CIS
- Number of recurrences
- Imaging: invasive, hydronephrosis, metastasis
- Kidney function and other medical problems

Intracavitary treatment of UTUC

- Intracavitary therapies include immunotherapy and chemotherapy
  - BCG, mitomycin C
- Questionable efficacy in reducing risk of UTUC following endoscopic management
- Difficulty with administration of intracavitary therapies
  - Antegrade or retrograde
  - Limited dwell time
  - Difficulties in adequate tissue exposure



BCG, bacillus Calmette–Guérin.

Roupret M, et al. Eur Urol. 2018;73:111-22. Raman JD, Park R. Expert Rev Anticancer Ther. 2017;17:545-54. Mandalapu RS, et al. World J Urol. 2017;35:355-65. Metcalfe M, et al. J Endourol. 2017;31:946-53.

First drug trial for UTUC in 2016

- Investigation of a drug–device combination
  - Drug: mitomycin C (MMC) is a chemotherapeutic agent
    - MMC has been used for decades (discovered in 1963)
  - Device: a new reverse polymer hydrogel
    - Liquid at cold temperature
    - Gels at body temperature
    - Dissolves slowly in liquid (urine)

- Chemoablation: **mitomycin gel** consists of a mitomycin containing reverse thermal hydrogel

Kleinmann N, et al. Lancet Oncol. 2020;21:776-85.

How does chemoablation with mitomycin gel work?

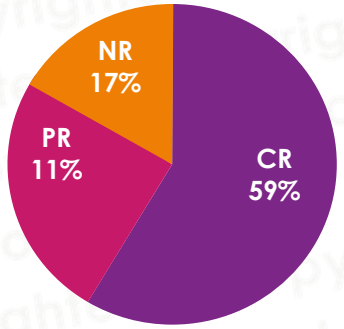
Optimizes exposure to mitomycin	• Increases the dwell time of mitomycin exposure in the upper tract • Prolonged exposure of a period of 4−6 hours vs 5 minutes
Anatomy-conforming technology	• Overcomes current treatment challenges by conforming to the complex upper urinary tract anatomy and enhancing coverage
Increased therapeutic index	• The hydrogel formulation consists of a higher amount of mitomycin compared to aqueous mitomycin in standard settings
Sustained drug delivery through slow release	• Slow dissolution through continuous urinary bathing results in the slow release of active mitomycin over several hours

Kokorovic A, Matin SF. Ther Adv Med Oncol. 2020;12:1758835920937950.
Kleinmann N, et al. Lancet Oncol. 2020;21:776-85.

OLYMPUS study: primary chemoablation of low-grade UTUC using intracavitary mitomycin gel

- **OLYMPUS response rates**
  - Response at primary disease evaluation[a] (primary endpoint n = 71; ITT)

CR	PR	NR
59%	11%	17%
42/71	8/71	12/34



- **Final analysis**
  - Consistent CR rate of 59% (95% CI 47–71; p < 0.0001)
  - Durability of response:
    - 89% at 6 months
    - 84% at 12 months
  - 34 of 71 were initially characterized as having an endoscopically unresectable tumor at baseline

Most common treatment-emergent adverse events (n = 71)

	Grade 1–2	Grade 3	Grade 4–5
Ureteric stenosis	35%	8%	0
Urinary tract infection	30%	3%	0
Hematuria	28%	3%	0
Flank pain	27%	3%	0
Nausea	23%	1%	0
Dysuria	21%	0	0
Renal impairment	18%	1%	0
Vomiting	15%	4%	0
Abdominal pain	17%	1%	0

Majority of AEs were mild-to-moderate

[a] At PDE, 6 patients had HG disease and 3 had indeterminate disease level.
AE, adverse event; CI, confidence interval; CR, complete response; ITT, intention to treat; NR, no response; OLYMPUS, Optimized DeLivery of Mitomycin for Primary UTUC Study; PDE, primary disease evaluation; PR, partial response.

Kleinmann N, et al. Lancet Oncol. 2020;21:776-85.

OLYMPUS: conclusions

- Primary chemoablation of LG UTUC
  - Feasible retrograde instillation via ureteral catheter
  - Efficacy data suggest primary chemoablation is efficacious with excellent durability of complete response
  - Mitomycin gel appears generally safe and well-tolerated to date (AEs similar to those reported with repeated UTUC endoscopy)

- First FDA approved therapy for the treatment of LG UTUC
- Further conclusions to be drawn upon completion of long-term follow-up

- An alternative option to retrograde treatment is percutaneous nephrolithotomy

Kleinmann N, et al. Lancet Oncol. 2020;21:776-85.
FDA approval Jelmyto™. Availablefrom: https://www.fda.gov/news-events/press-announcements/fda-approves-first-therapy-treatment-low-grade-upper-tract-urothelial-cancer. Accessed August 2020.

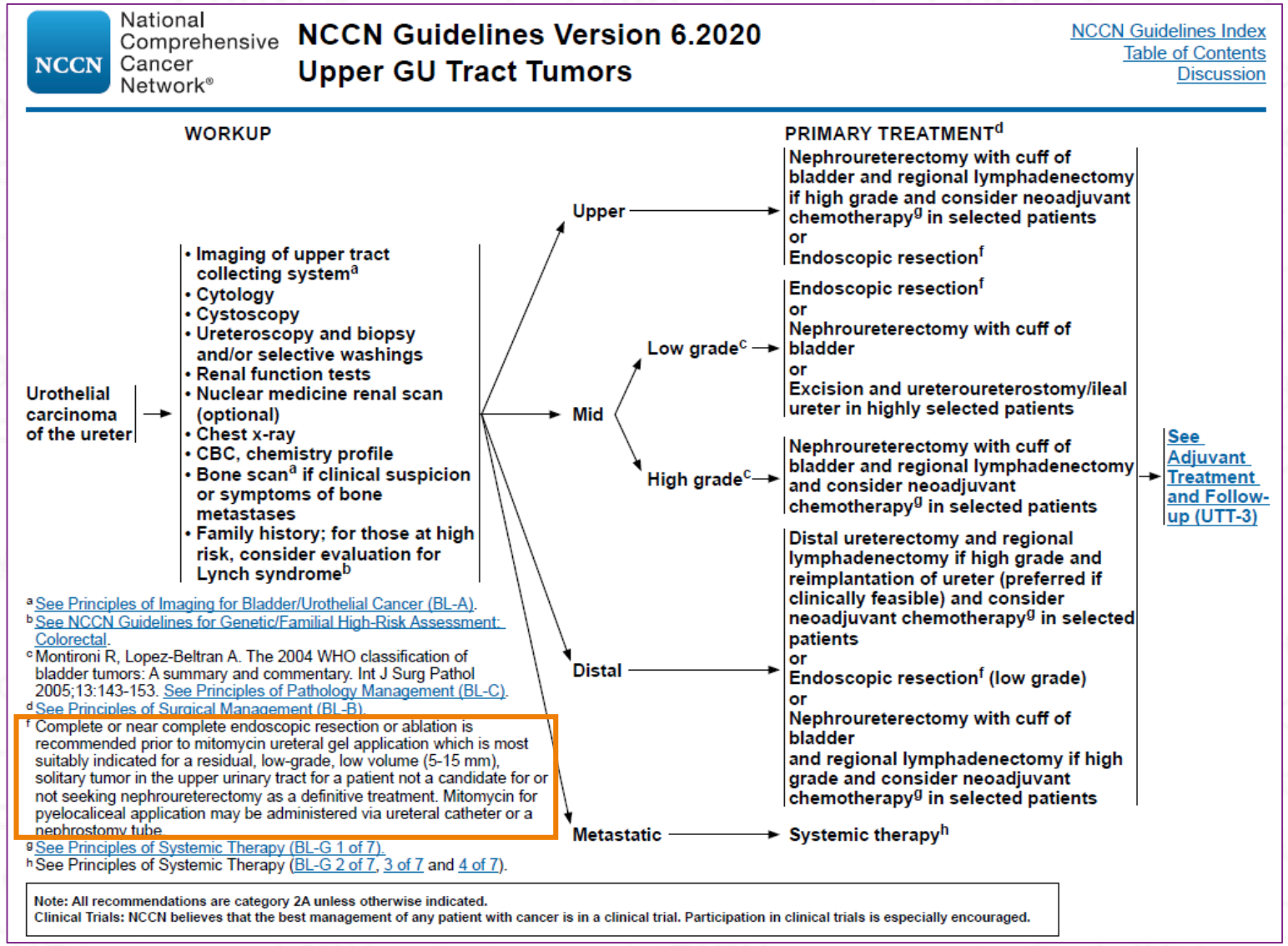
AE, adverse event; FDA, US Food and Drug Administration.

Practical recommendations for chemoablation in the clinic

- Important considerations include
  - Location in the kidney (kidney pelvis, uni-/bilateral, solitary kidney)
  - Size and number of tumors (small tumors 0.5–1.5 cm)
  - HG vs LG, particularly for patients with low-risk LG disease
  - Number of recurrences
  - Kidney function and other medical problems

- Nephron-sparing is the preferred approach to greatly increasing kidney preservation
  - Chemoablation may provide durable disease-free response
  - Potential to change how we treat LG disease
    - May reduce or eliminate the need for multiple endoscopies

Guideline recommendations for UTUC



National Comprehensive Cancer Network®

NCCN Guidelines Version 6.2020
Upper GU Tract Tumors

NCCN Guidelines Index
Table of Contents
Discussion

WORKUP

Urothelial carcinoma of the ureter

- Imaging of upper tract collecting system[a]
- Cytology
- Cystoscopy
- Ureteroscopy and biopsy and/or selective washings
- Renal function tests
- Nuclear medicine renal scan (optional)
- Chest x-ray
- CBC, chemistry profile
- Bone scan[a] if clinical suspicion or symptoms of bone metastases
- Family history; for those at high risk, consider evaluation for Lynch syndrome[b]

PRIMARY TREATMENT[d]

Upper
Nephroureterectomy with cuff of bladder and regional lymphadenectomy if high grade and consider neoadjuvant chemotherapy[g] in selected patients
or
Endoscopic resection[f]

Mid

Low grade[c]
Endoscopic resection[f]
or
Nephroureterectomy with cuff of bladder
or
Excision and ureteroureterostomy/ileal ureter in highly selected patients

High grade[c]
Nephroureterectomy with cuff of bladder and regional lymphadenectomy and consider neoadjuvant chemotherapy[g] in selected patients

Distal
Distal ureterectomy and regional lymphadenectomy if high grade and reimplantation of ureter (preferred if clinically feasible) and consider neoadjuvant chemotherapy[g] in selected patients
or
Endoscopic resection[f] (low grade)
or
Nephroureterectomy with cuff of bladder
and regional lymphadenectomy if high grade and consider neoadjuvant chemotherapy[g] in selected patients

Metastatic
Systemic therapy[h]

See Adjuvant Treatment and Follow-up (UTT-3)

[a] See Principles of Imaging for Bladder/Urothelial Cancer (BL-A).
[b] See NCCN Guidelines for Genetic/Familial High-Risk Assessment: Colorectal.
[c] Montironi R, Lopez-Beltran A. The 2004 WHO classification of bladder tumors: A summary and commentary. Int J Surg Pathol 2005;13:143-153. See Principles of Pathology Management (BL-C).
[d] See Principles of Surgical Management (BL-B).
[f] Complete or near complete endoscopic resection or ablation is recommended prior to mitomycin ureteral gel application which is most suitably indicated for a residual, low-grade, low volume (5-15 mm), solitary tumor in the upper urinary tract for a patient not a candidate for or not seeking nephroureterectomy as a definitive treatment. Mitomycin for pyelocaliceal application may be administered via ureteral catheter or a nephrostomy tube.
[g] See Principles of Systemic Therapy (BL-G 1 of 7).
[h] See Principles of Systemic Therapy (BL-G 2 of 7, 3 of 7 and 4 of 7).

Note: All recommendations are category 2A unless otherwise indicated.
Clinical Trials: NCCN believes that the best management of any patient with cancer is in a clinical trial. Participation in clinical trials is especially encouraged.

NCCN Guidelines Version 6.2020. Available from: https://www.nccn.org/professionals/physician_gls/pdf/bladder.pdf. Accessed August 2020.

Summary

- There is a lack of uniform recommendations for diagnosis, treatment, and follow-up of UTUC
- RNU remains the cornerstone of management for HG UTUC, but is less clear for LG UTUC
- Nephron-sparing options provide an important alternative to RNU for low-risk LG UTUC; however, challenges remain using these techniques
- In LG disease, nephron-sparing modalities are recommended for patients with renal insufficiency, bilateral UTUC, a solitary kidney, or for those patients where RNU is otherwise contraindicated
- Intracavitary therapies are generally utilized as adjuvant therapy in UTUC, but have a limited role in LG disease
- Chemoablation with intracavitary mitomycin gel is a promising alternative kidney-sparing approach for LG UTUC

This activity was developed by Ology Medical Education and supported by an independent educational grant from UroGen Pharma.

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