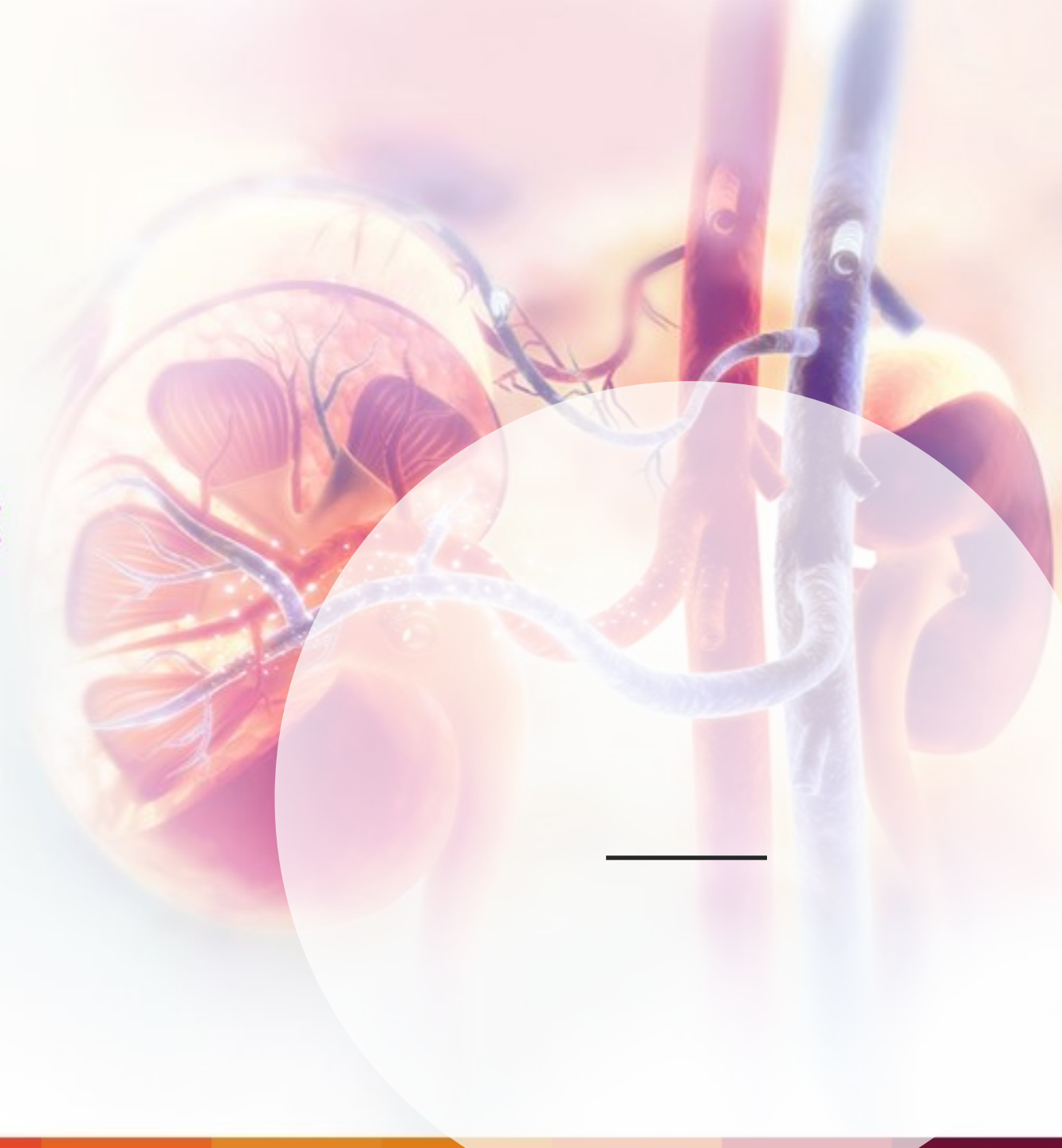


Expert insights on novel treatment options for UTUC

Roundtable discussion



Disclaimer

- The views expressed in the following presentations are those of the individual presenting speakers
- The presentations may discuss therapeutic products that have not been approved, or off-label use of certain products
- These presentations are for educational purposes only and should not be reproduced or distributed in any way
 - *If you wish to reproduce, store in a retrieval system, transmit in any form or by any means, electronic, mechanical, photocopying, recording, or otherwise, any part of the material presented, you will need to obtain all the necessary permissions by writing to the publisher, the original author, or any other current copyright owner*
- Ology Medical Education emphasizes that the content of these materials/this educational activity is provided for general educational purposes only, and should not in any way be considered as advisory; it is the responsibility of the health care professional to verify all information and data before treating patients or using any therapies described

Faculty



Seth Lerner, MD, FACS

Professor of Urology
Director, Urologic Oncology
Director, Multidisciplinary Bladder
Cancer Program
Vice-Chair of Faculty Affairs, Scott
Department of Urology
Baylor College of Medicine
Houston, TX, USA



Surena Matin, MD

Professor, Department of Urology
Division of Surgery
University of Texas
MD Anderson Cancer Center
Houston, TX, USA



Phillip Pierorazio, MD

Associate Professor of Urology and Oncology
Brady Urological Institute
Johns Hopkins University
Baltimore, MD, USA

Agenda

Dr Seth Lerner

Unmet needs and
introduction to the
management of
UTUC

Dr Surena Matin

Staging, grading,
and risk stratification
of UTUC

Dr Phillip Pierorazio

New and emerging
treatment
approaches for
low-grade UTUC
and clinical
implications

Moderated by Dr Seth Lerner

Unmet needs and introduction to the management of UTUC



UTUC assessment

Ureteropyeloscopy

- Visual assessment of upper urothelial tract and renal pelvis



Cytology and biopsy

- High-grade cytology confirms UC diagnosis
- High-grade biopsy has good concordance with final pathology (91%)¹ and is associated with invasive disease

21% of cases are under-staged/under-graded by visual inspection alone²

Renal preservation

- **Imperative** in some cases
 - Functional/anatomic, solitary kidney, CKD
 - Bilateral disease
 - Comorbidity/high surgical risk
- **Elective** in others
 - Low-grade disease
 - Small-volume, high-grade distal ureter tumor
 - CR after neoadjuvant chemotherapy
 - Risk of upstaging with delay in RNU

Intracavitary therapy

- Chemotherapy/immunotherapy delivered via percutaneous nephrostomy or ureteral catheter
 - Mitomycin C, BCG, epirubicin, thiotepa¹
- Marker lesion trial is a standard of care for testing activity of new drugs for intravesical therapy
 - Review of 23 studies with > 1,200 patients²
 - 30–50% of patients achieved CR
 - Highest response rate was achieved with apaziquone in intermediate-risk disease (67%)
 - CR was associated with longer RFS
 - No progression was observed in patients with intermediate-risk disease

Discussion points

- Intracavitary therapy can reduce the recurrence rate associated with endoscopic management
- Frequent URS can be a burden to patients and caregivers
- Intravesical therapy after URS can reduce the risk of recurrence in the bladder
- Low-grade UTUC does not represent a homogenous population
 - Some patients respond well to endoscopic management, others have rapid proliferating disease
 - Identifying which patients require more than endoscopic therapy is challenging
- Intracavitary treatment (chemotherapy or immunotherapy) may be used to reduce risk of recurrence

Staging, grading, and risk stratification of UTUC



Two modalities for staging and grading

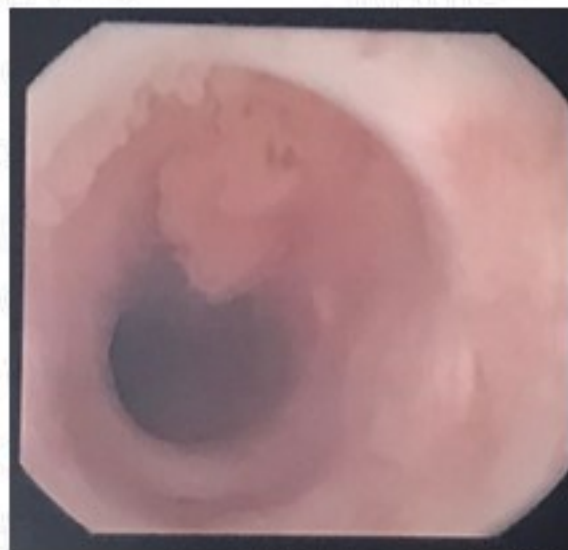
Imaging^{1,2}

- CTU can identify filling defect, size, number, infiltration, lymph nodes, and status of contralateral kidney
- CT chest/chest X-ray can rule out metastases and establish a baseline



Cystoscopy + URS^{1,2}

- Cystoscopy can confirm clear bladder and assess bladder capacity if considering psoas hitch or Boari flap for a distal ureter tumor
- URS enables biopsy for grading and can also assess size (better than CT), architecture, and multifocality



Images provided by Dr Matin.

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

2. Mandalapu RS, et al. World J Urol. 2017;35:355-65.

Tumor architecture and biopsy grade are important determinants of outcome

Endoscopic biopsy performance

- Biopsy diagnostic yield: 89%¹
- Sensitivity for UTUC: 84%¹
- Grading concordance between biopsy and RNU specimen: 69–91%²
- Proportion of low-grade tumors subsequently upgraded: 33%¹

Technical factors that influence biopsy adequacy³

- Use of access sheaths
- Number of samples
- Biopsy technique
- Sessile tumors

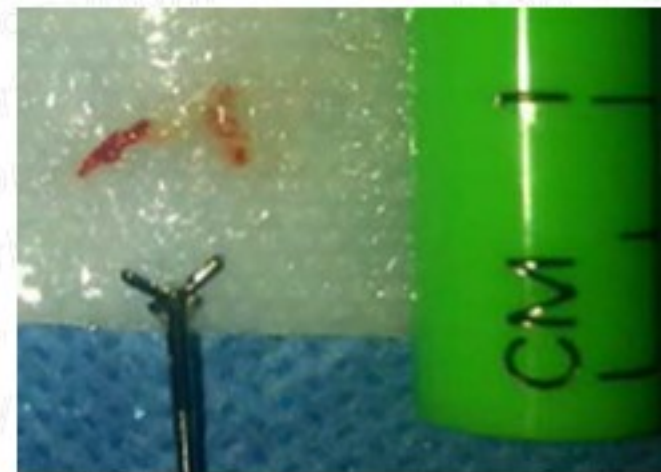
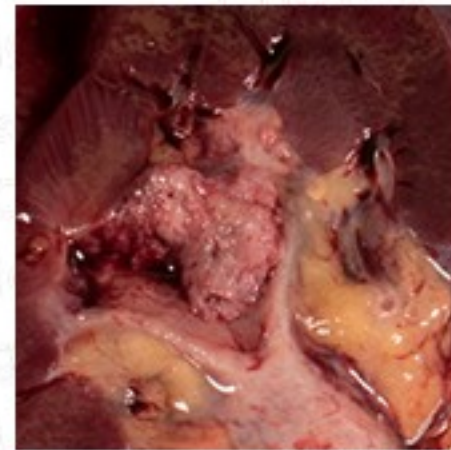
1. Freund JE, et al. J Endourol. 2020;34:907-13.

2. Cutress ML, et al. BJU Int. 2012;110:614-28.

3. Petros FG, et al. Urol Clin North Am. 2018;45:267-86.

Limitations: current methods are inadequate for clinical staging

- CT imaging may miss T3 disease
 - Imaging showed no invasion, but pathology of RNU specimen indicated sinus invasion (pT3)
- URS biopsies are superficial and cannot reliably rule out invasion or assess depth of invasion
- Diagnosing “muscle-invasive UTUC” is not a clinical reality



Tools for biopsy and resection



3-F cup biopsy forceps

Larger specimens can be obtained with the push technique



1.7-F nitinol basket

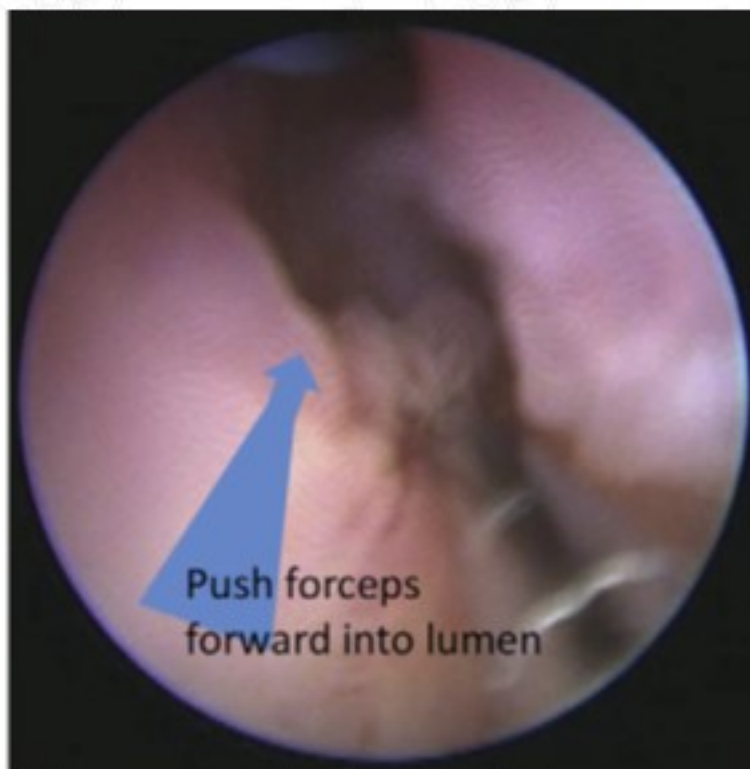
Mainly for renal pelvis or calyces/lower pole and if hematuria is present



3-F steel wire basket

Ideal for larger tumors in the ureter and if no hematuria is present

The push technique helps obtain larger specimens



This technique can be repeated multiple times

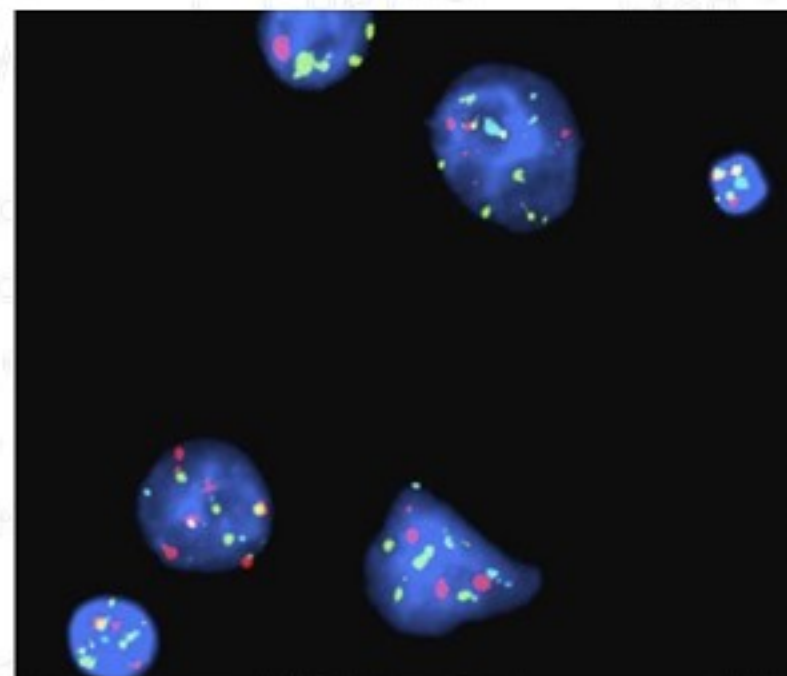
What about urinary markers?

- Cytology

- Upper-tract washing can be valuable as an adjunct to biopsy if performed as selective washing^{1,2}
- This can compensate for nondiagnostic/equivocal biopsy^{1,2}
- Voided cytology has a limited role in UTUC³
- Can be only indication of UTCIS (+ washing with negative high-quality URS)⁴

- FISH

- Possibly higher sensitivity than cytology, but less specificity⁵
- May be used after upper-tract BCG treatment (predictive)



1. Margolin EJ, et al. J Urol. 2018;199:1440-5.
2. Kleinmann N, et al. J Endourol. 2013;27:1450-4.
3. Messer J, et al. BJU Int. 2011;108:701-5.
4. Redrow GP, et al. J Urol. 2017;197:287-295.
5. Mian C, et al. Eur Urol. 2010;58:288-92.

Risk stratification: EAU criteria

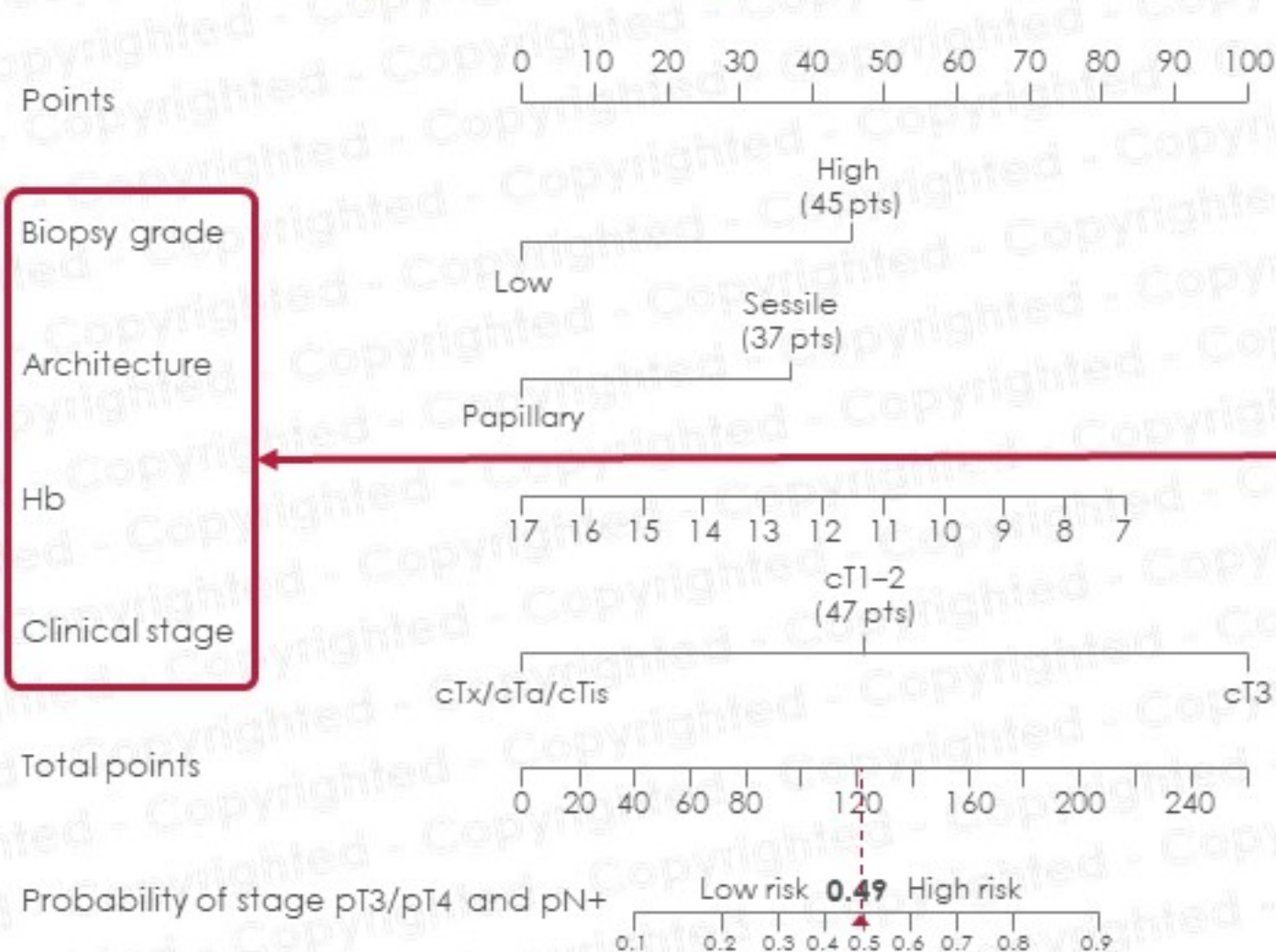
Low-risk disease

- Unifocal
 - Tumor size < 2 cm
 - Low-grade cytology
 - Low-grade URS biopsy
 - No invasive aspect on CTU
- Represents "very low-risk" disease
 - Broad consensus
 - Indicates low-risk for progression and good chance of successful URS management

High-risk disease

- Multifocal
 - Tumor size > 2 cm
 - High-grade cytology
 - High-grade URS biopsy
 - Hydronephrosis
 - Prior radical cystectomy for bladder cancer
 - Variant histology
- Multiple criteria interactions have not been validated

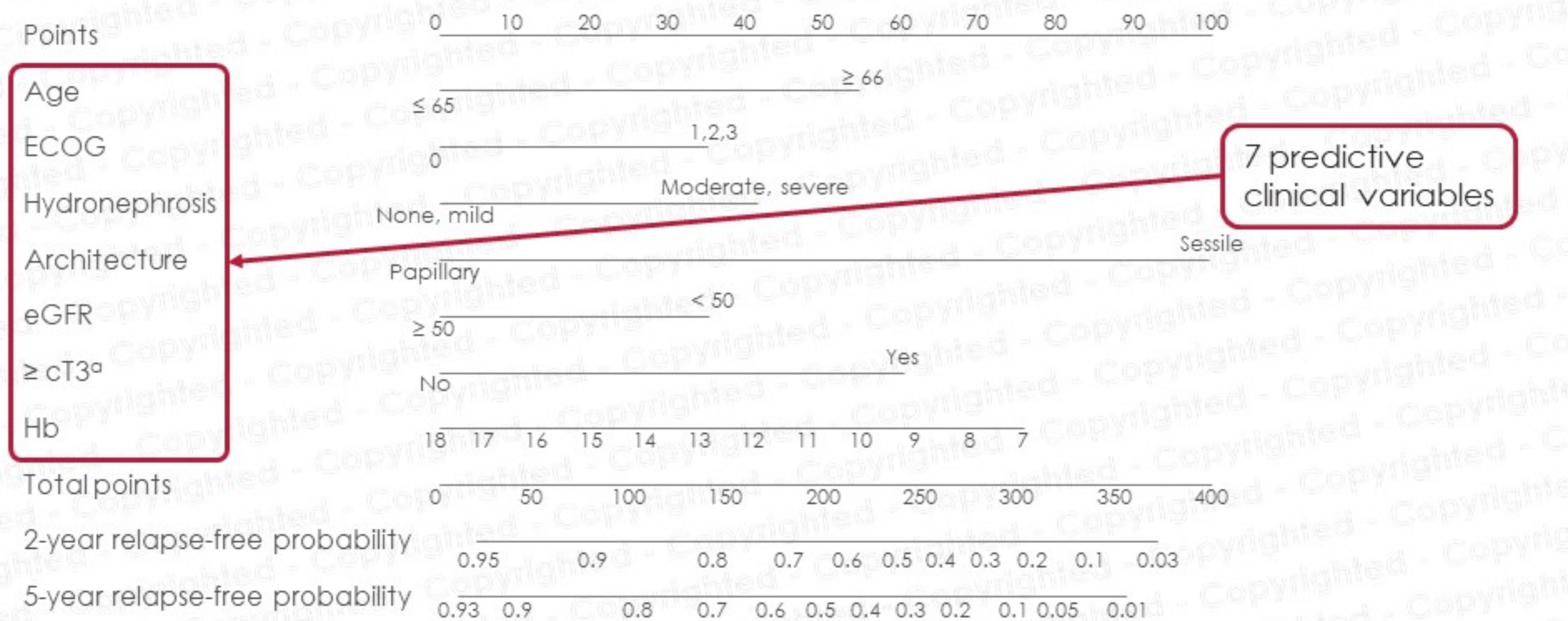
Preoperative nomogram to predict non-organ-confined disease (pT3-4, N+)



- N = 566
 - n = 396 development
 - n = 170 validation
- 23 variables evaluated
- Accuracy 82%

4 independently predictive clinical variables

Preoperative nomogram to predict disease recurrence after RNU (patients with high-grade UTUC)



^a Based on imaging studies.

ECOG, Eastern Cooperative Oncology Group; eGFR, estimated glomerular filtration rate.

Risks and benefits of kidney preservation (URS) vs RNU

Risks

- Upper-tract recurrence: 15–90%
- Bladder recurrence: 12–70%
- Multiple procedures may be required

Benefits

- Favorable OS: 35–100%
- Favorable CSS: 70–100%
- Preserves kidney function
- Low rate of salvage RNU: 0–30%

Discussion points

- Risk of recurrence can be minimized with good endoscopic practice
 - Remove/ablate as much of the primary tumor as possible
 - Use access sheath to maximize biopsy sampling, facilitate irrigation and multiple maneuvers, and minimize seeding”
- Indwelling ureteral stents: do they increase recurrence risk?
- Make sure patients are aware of both benefits and risks of kidney-sparing approaches, including the possible need for multiple procedures



New and emerging treatment approaches for low-grade UTUC and clinical implications

Management principles for low-risk, low-grade UTUC

1

Treat primary tumor

2

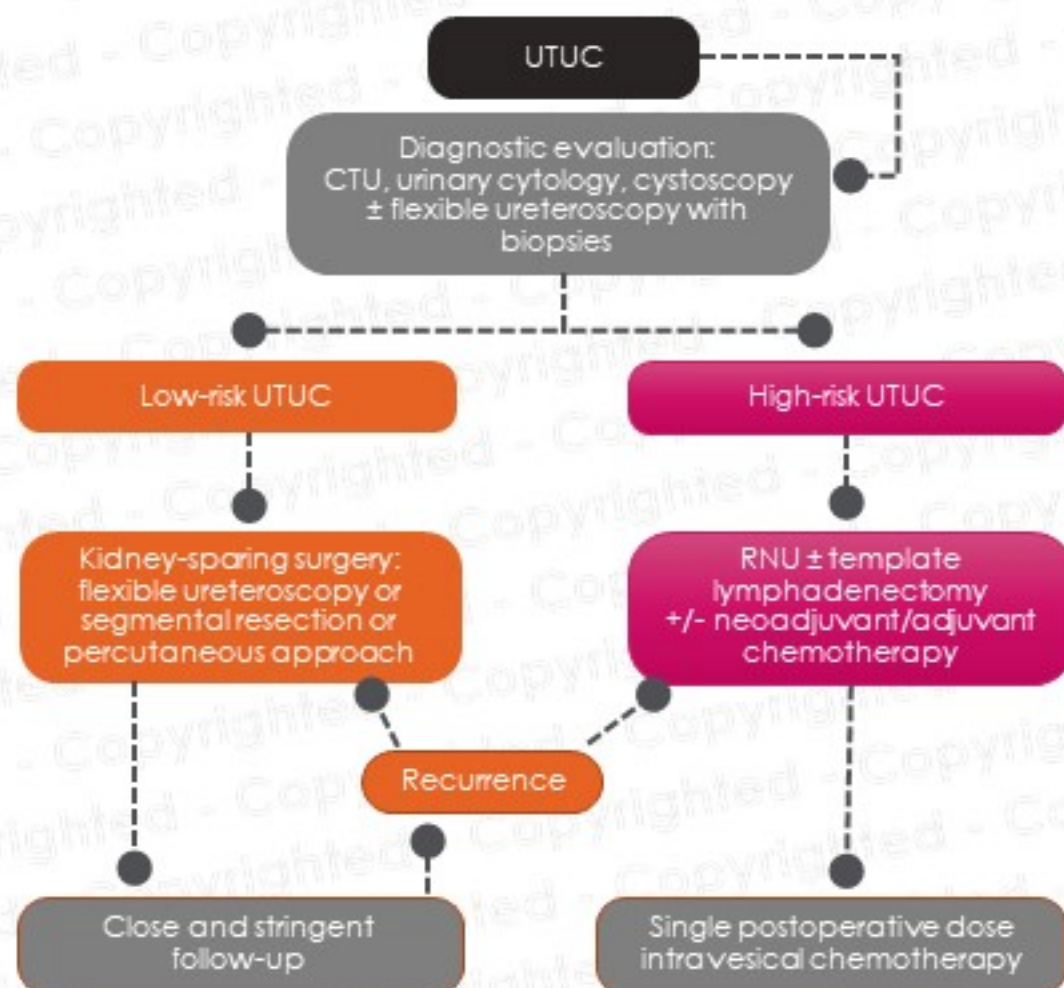
Manage recurrences

3

Recognize low risk of
progression to
high-grade or
metastatic disease

Management options

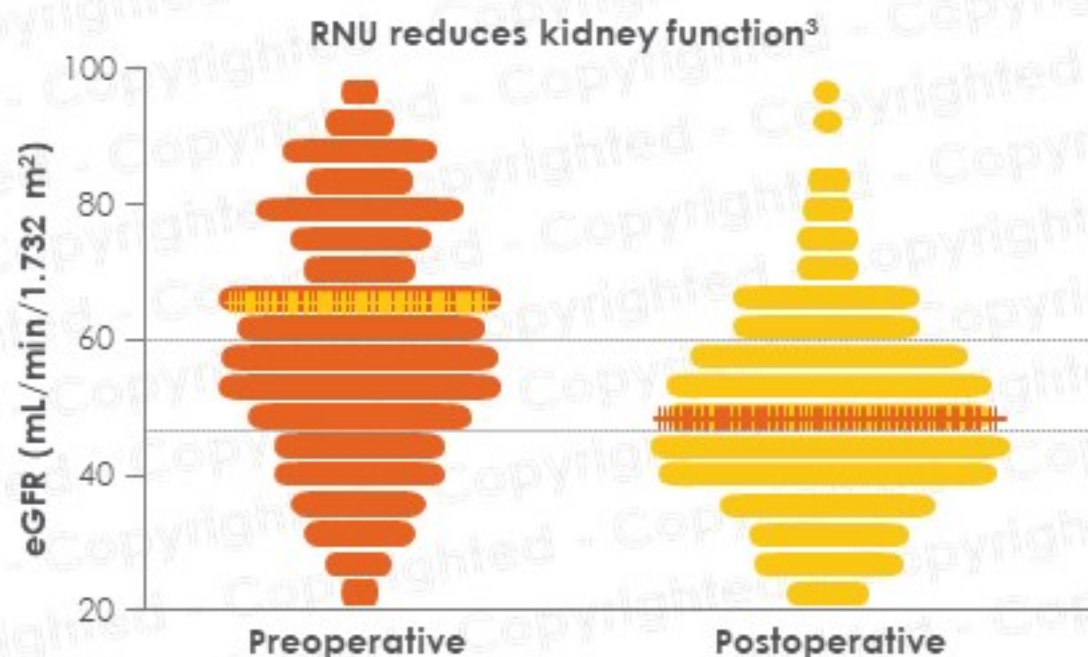
- RNU is the gold standard and last resort
- Kidney-sparing surgery
 - Endoscopic management
 - Ablation and/or resection
 - Ureteroscopy
 - Percutaneous approach
 - Adjuvant intracavitary therapies
 - BCG, mitomycin C
 - Retrograde or antegrade
 - Chemoablation
 - OLYMPUS trial



Challenges in the management of low-grade disease

Limitations of RNU

- Increased risk of: complications, severe renal insufficiency, cardiovascular events, mortality¹⁻⁴
- Risk increases with age¹⁻³



Issues with endoscopic literature

- No RCTs comparing endoscopic management with RNU⁴
- Strong selection bias for favorable tumor characteristics in many endoscopically treated groups⁴
- Variation in medical comorbidity and indication for treatment
- Biopsy verification inconsistent
- Limited follow-up (typically < 3 years)⁴

1. Raman JD, et al. Urol Oncol. 2014;32:47.e9-14.

2. Jeldres C, et al. Urology. 2010;75:315-20.

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

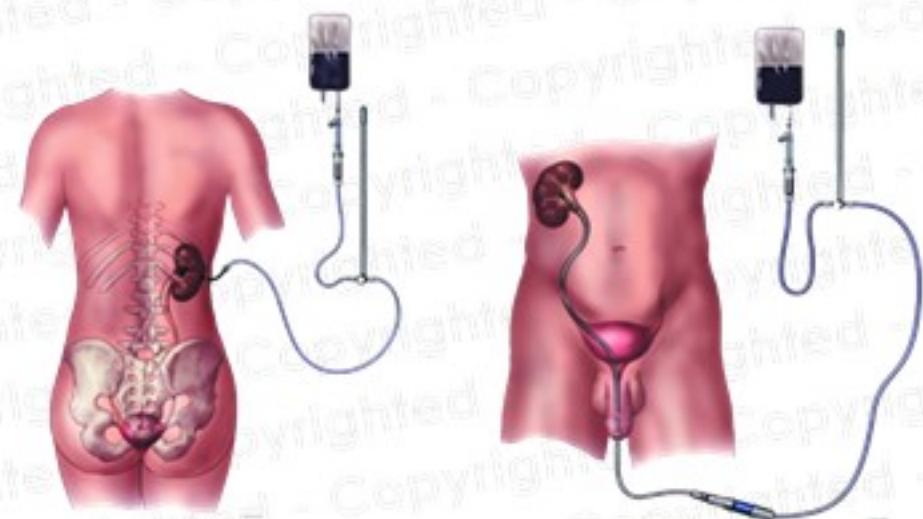
4. Raman JD, Park R. Expert Rev Anticancer Ther. 2017;17:545-54.

Endoscopic management: literature review

	Ureteroscopy, % 22 studies (736 patients)	Percutaneous management, % 11 studies (288 patients)
Overall mortality	28	21
Disease-specific mortality	9	11
Failed endoscopic management	24	32
Progression to RNU	19	22
Progression of disease	15	17
Metastatic disease	9	NR (tumor tract seeding, n = 1)
Complication rate	14	27
Stricture rate	11	

Challenges with adjuvant intracavitary therapy

- Poor quality and inconsistent efficacy data¹
 - Mitomycin C: response rates 35%²
 - BCG: response rates 64–100% in CIS³
- Mode of delivery⁴
 - Lack of dwell time
 - Need reliable access to the upper tract
- Complications^{1,3}



1. Carmignani L, et al. Rev Urol. 2013;15:145-53.

2. Mostafid AH, et al. BJU Int. 2020;125:817-26.

3. Park BH, Jeon SS. Korean J Urol. 2013;54:426-32.

4. Mandalapu RS et al. World J Urol. 2017;35:355-65.

New developments in UTUC: rationale for chemoablation using mitomycin gel

- Mitomycin gel is a reverse-thermal gel polymer that is
 - Liquid at low temperature
 - Solid/gel at body temperature
- Mitomycin gel may promote
 - Delivery into the upper urothelial tract by conforming to anatomy
 - Retention of drug while preventing rapid excretion

Mitomycin gel in UTUC: proof of concept

- Compassionate-use study of mitomycin gel (UGN-101)
- Methods
 - 22 patients received 6 weekly instillations of UGN-101 via ureteral catheter or percutaneous nephrostomy
- Outcomes in low-grade disease (n = 18)
 - CR 44% (8/18)
 - PR 28% (5/18)



Images courtesy of Dr J Gregory Wirth.
Kleinmann N, et al. Bladder Cancer. 2019;5:21-9.

Phase 3 OLYMPUS trial of mitomycin gel in low-grade UTUC

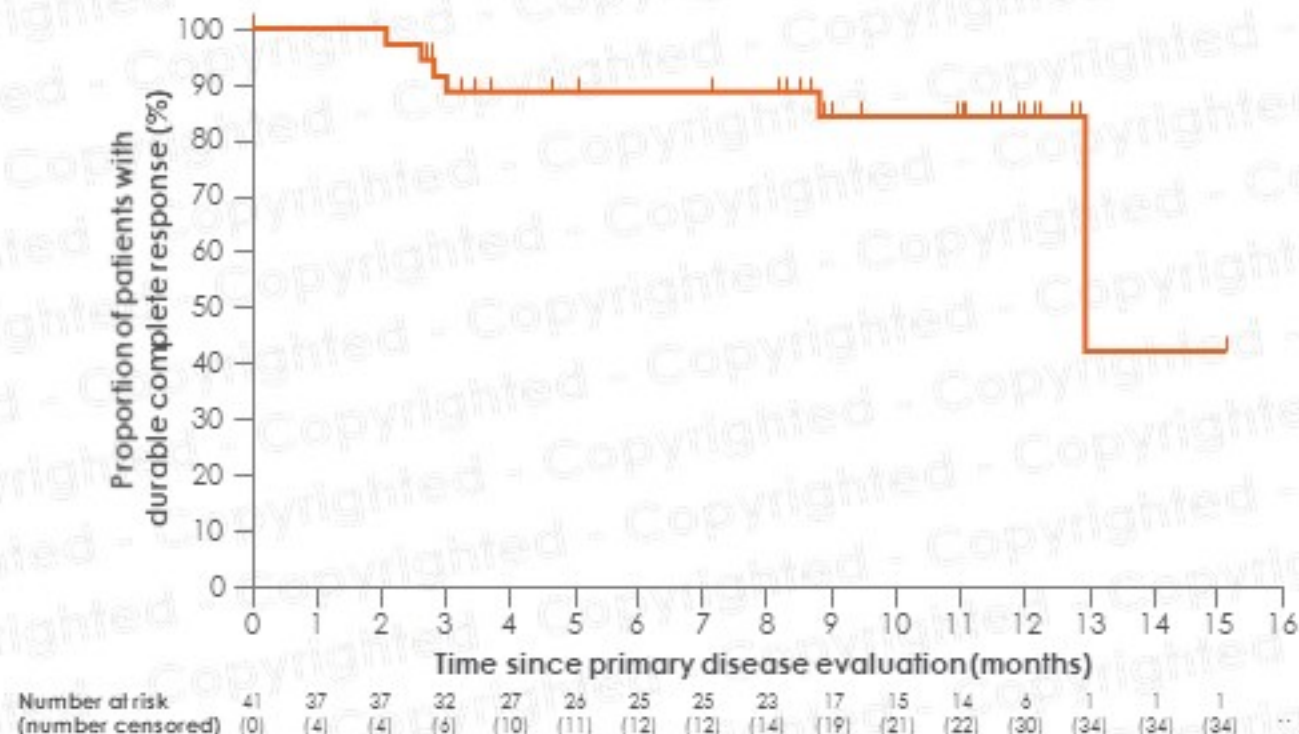
- Design:** prospective phase 3, open-label, single-arm trial in patients with low-grade UTUC



- Treatment:** 6 weekly instillations of mitomycin gel
- Primary endpoint:** CR rate at Month 3

OLYMPUS: efficacy of mitomycin gel in low-grade UTUC

Primary disease evaluation results	n (%)
Complete response	42 (59)
No complete response	29 (41)
Partial response	8 (11)
No response	12 (17)
High-grade disease	6 (8)
Indeterminate	3 (4)
Unresectable at baseline (n = 34)	20 (59)



- Most responses were rapid (by Month 3) and durable (~ 1 year)
- "High-grade" likely represents survival of high-grade component (vs disease transformation)

OLYMPUS: safety of mitomycin gel in low-grade UTUC

Event, %	TEAEs in $\geq 15\%$ of patients (n=71)	
	Grade 1 or 2	Grade 3
Ureteric stenosis	35	8
UTI	30	3
Hematuria	28	3
Flank pain	27	3
Nausea	23	1
Dysuria	21	0
Renal impairment	18	1
Vomiting	15	4
Abdominal pain	17	1
Hydronephrosis	13	6
Fatigue	15	0

- Acute kidney injury (6% grade 1 or 2, 1% grade 3)
- 1 grade 4 event (urosepsis) was unrelated to treatment
- 3 deaths (cerebrovascular accident, failure to thrive, unknown) were unrelated to treatment
- Most TEAEs occurred after the third instillation
- Most were transient and resolved spontaneously or with use of steroids

Other novel developments for low-grade UTUC

Laser ablation

- Thulium lasers
- MOSES™ and other laser modulation technologies

Topical chemotherapy

- Combination chemotherapy (gemcitabine/docetaxel)
- Maintenance regimens

Systemic therapies

- Pembrolizumab (bladder cancer)
- Erdafitinib (FGFR3 inhibitor)

Novel delivery of agents/diagnostics

- Targeted molecules
- Nanotechnologies

Discussion points

- Mitomycin gel represents a new treatment option for patients with low-grade UTUC
 - May help to reduce recurrence rate and number of procedures
 - Ureteric strictures can occur; may be managed with steroids or treatment delay
 - May be an option for patients with unresectable disease
 - Maintenance: if recurrence occurs during maintenance, options include other intracavitary chemotherapy agents following tumor ablation

Discussion points (cont.)

- Mitomycin gel could be used potentially as an adjuvant treatment after endoscopic therapy (off-label use)
- Treatment options for patients with a solitary kidney
 - High-grade: consider RNU or percutaneous resection with intracavitary BCG
 - Low-grade: multiple options are available (percutaneous resection, endoscopic resection, chemoablation adjuvant therapy)

Discussion points (cont.)

- Approaches to follow-up
 - Dr Martin
 - Initial follow-up: URS every 3 months for the first 6 months
 - If no evidence of disease: switch to imaging only every 3 months for 6 months
 - If still no evidence of disease: imaging every 6 months
 - Dr Pierorazio
 - Follow-up is individualized to each patient
 - If visible tumor: schedule second URS in 3 months
 - If no visible tumor: alternating URS and imaging every 3 months
 - After 1 year, imaging every 6 months/URS every 12 months

Key messages

- Accurate staging and grading of UTUC is challenging but remains the cornerstone to identifying appropriate patients for kidney-preserving treatments
- The experience of the OLYMPUS trial may bring a resurgence of intracavitary therapy for patients with low-grade disease; this provides the potential for both chemoablation and adjuvant treatment in the post-ablation setting, and a real opportunity for kidney preservation

See the supplemental information under the “Resources” tab for further information on the endoscopic management of low-grade UTUC, including an algorithm to help guide decisions on care



Thank you for participating in this activity



This activity was developed by Ology Medical Education and is supported by educational funding provided by UroGen Pharma.

More educational programs are available on our website:

<https://ologyeducation.org>