Upper tract urothelial carcinoma (UTUC)

W. Kassouf, MD, CM, FRCS
Professor of Urology, McGill University Health Center
Vice Chair, Dept. of Surgery, McGill University
• **Upper tract urothelial carcinoma consortium**
  - International collaboration
  - Includes 14 centers from USA, Canada, Europe, and Japan
  - Some slides courtesy of Dr Shahrokh Shariat

• **Canadian upper tract collaboration**

  Includes most academic centers in Canada:
  
  McGill (Kassouf)  Dalhousie (Rendon)
  Montreal (Lattouf, Saad)  Alberta (Fairey/Jacobsen)
  Laval (Lacombe/Fradet)  UBC (Black/So)
  McMasters (Kapoor)  Ottawa (Cagiannos)
  Western (Izawa/Chin)  Manitoba (Drachenberg)
Facts of a rare disease

• Incidence
  – ~6% of all urothelial tumors
  – ~8% of all renal tumors
  – Estimated annual incidence: 1-2/100,000

• Presentation
  – 2-6% recurrence in the contralateral UTUC
  – 65% pyelocaliceal
  – 35% ureteral: 5% proximal, 25% middle, 70% distal

• UTUC and bladder cancer
  – 8-13% concurrent bladder cancer
  – 30-51% recurrence in bladder (multifocality, field effect, seeding)

Siegel et al., CA Cancer J Clin 2015; Chromecki, Shariat et al., Nature Rev 2011
Lynch Syndrome: A Primer for Urologists and Panel Recommendations

Maureen Mork, Scott G. Hubosky, Morgan Rouprêt, Vitaly Margulis, Jay Raman, Yair Lotan, Timothy O’Brien, Nancy You, Shahrokh F. Shariat* and Surena F. Matin†

**UTUC and any 1 of the following:**
1. Diagnosis <60 years of age
2. Family history of: UTUC, colon cancer diagnosis <60 years, endometrial cancer
3. Personal history of colon or endometrial cancer

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1. **Immunohistochemistry**
   - for MLH1, MSH2, MSH6, PMS2

2. **PCR Molecular Studies**
   - for allelic shifts in microsatellite markers BAT25, BAT26, D2S123, DSS346, D17S250 and (BAT 40 and TGFBR3)**

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**Clinical suspicion**

**High**

**Absence of protein**

**MSI High**

**MSI Stable or Low**

**Clinical suspicion**

**High**

**Low**

**Referral for genetic counseling**
Imaging

- **Multidetector CT Urography (excretory phase!)**
  - Gold standard and replaced IVP

<table>
<thead>
<tr>
<th>Size</th>
<th>Sensitivity</th>
<th>Specificity</th>
</tr>
</thead>
<tbody>
<tr>
<td>5-10 mm</td>
<td>96%</td>
<td>99%</td>
</tr>
<tr>
<td>&lt;5 mm</td>
<td>89%</td>
<td>-</td>
</tr>
<tr>
<td>&lt;3 mm</td>
<td>40%</td>
<td>-</td>
</tr>
</tbody>
</table>

- **MRI Urography**
  - Detection rate: 75% for tumors <2 cm
  - CI: severe renal impairment (<30 ml/min creat clearance)

Nephrogenic systemic fibrosis
Cystoscopy & cytology

• Positive urine cytology suggestive of UTUC if cysto NL & no CIS bladder & prostatic urethra
• Cytology less sensitive for UTUC than for bladder cancer
  • Better if performed in situ
• Positive cytology associated with ≥pT2 UTUC
## FISH

<table>
<thead>
<tr>
<th></th>
<th>Cytology</th>
<th>FISH</th>
<th>( N )</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Yu, Onco lett</td>
<td>2016</td>
<td>42%</td>
<td>84%</td>
<td>125</td>
</tr>
<tr>
<td>Huang, Neoplasma</td>
<td>2012</td>
<td>-</td>
<td>100%</td>
<td>285</td>
</tr>
<tr>
<td>Xu, Urol</td>
<td>2011</td>
<td>45%</td>
<td>79%</td>
<td>71</td>
</tr>
<tr>
<td>Mian, Eur Urol</td>
<td>2010</td>
<td>21%</td>
<td>100%</td>
<td>55</td>
</tr>
<tr>
<td>Johannes, J Urol</td>
<td>2010</td>
<td>18%</td>
<td>54%</td>
<td>35</td>
</tr>
<tr>
<td>Luo, Cancer Gen Cyto</td>
<td>2009</td>
<td>24%</td>
<td>86%</td>
<td>21</td>
</tr>
<tr>
<td>Marin-Aguilera, Eur Urol</td>
<td>2007</td>
<td>36%</td>
<td>77%</td>
<td>49</td>
</tr>
<tr>
<td>Akkad, Urology</td>
<td>2007</td>
<td>60%</td>
<td>88%</td>
<td>16</td>
</tr>
</tbody>
</table>

- Results for early detection are promising
- Less useful for surveillance because of higher false +ve rate
Indications for Conservative Management (ureteroscopy or percutaneous)

- No evidence of infiltrative lesion on imaging
- Low grade tumor on biopsy
- Negative cytology
- Unifocal tumor
- Small tumor
- Papillary

Agreement to close follow-up with repeated ureteroscopies
EAU: Risk Stratification of UTUC

ICUD-SIU 2016

* All of these factors need to be present
** Any of these factors need to be present

EUA 2015 Guidelines
### Upper Tract Urothelial Carcinoma Grading Evaluation

**TABLE 4-6** The accuracy of grading in ureteroscopic biopsies during diagnosis of UTUC

<table>
<thead>
<tr>
<th>Reference</th>
<th>Number of UTUC cases (n)</th>
<th>Biopsies diagnostic n (%)</th>
<th>Grading correct n (%)</th>
<th>Number of low-grade tumours upgraded n (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Guarnizo et al.</td>
<td>45</td>
<td>40 (89)</td>
<td>31 (78)</td>
<td>5 (19)*</td>
</tr>
<tr>
<td>Shiraishi et al.</td>
<td>40</td>
<td>35 (87.5)</td>
<td>18 (58)</td>
<td>0 (0)</td>
</tr>
<tr>
<td>Smith et al.</td>
<td>65</td>
<td>41 (63)</td>
<td></td>
<td>24 (43)</td>
</tr>
<tr>
<td>Williams et al.</td>
<td>30</td>
<td>30 (100)</td>
<td>17 (56.7)</td>
<td>3 (50)*</td>
</tr>
<tr>
<td>Wang et al.</td>
<td>184</td>
<td>48 (26)</td>
<td>83 (45)</td>
<td>23 (96)</td>
</tr>
<tr>
<td>Keeley et al.</td>
<td>51</td>
<td>42 (82.4)*</td>
<td>38 (90)</td>
<td>(10)</td>
</tr>
<tr>
<td>Skolarikos et al.</td>
<td>62</td>
<td>51 (82)</td>
<td>35 (69)</td>
<td>No G1 was upgraded to G3, G2 unknown</td>
</tr>
<tr>
<td><strong>OVERALL</strong></td>
<td>477</td>
<td>246/412 (59.7)</td>
<td>236/477 (55.1)</td>
<td>(0–96)</td>
</tr>
</tbody>
</table>

*Upgrading was from G1 to G2, but 0% to G3. †Of 6 G1 on biopsy, two were G2 and three G3; of 17 G2 on biopsy, 13 were G2 and 4 G3; of 4 G3 on biopsy, 1 was G2. ‡Diagnostic was performed with cytology in eight cases, with cell block in 29 cases, and with routine histopathology in five cases.
Any role of upper tract instillations (MMC or BCG)?
## BCG as adjuvant after tumor resection

<table>
<thead>
<tr>
<th>Study (year)</th>
<th>Patients, n (number of renal units treated)</th>
<th>Follow-up period</th>
<th>Technique of resection</th>
<th>Route of BCG administration</th>
<th>Tumor stage/grade</th>
<th>Results</th>
</tr>
</thead>
<tbody>
<tr>
<td>Schoenberg et al. (1991)</td>
<td>9 patients (9 units)</td>
<td>Mean: 24 months or until death</td>
<td>Percutaneous and retrograde through indwelling stent</td>
<td>Percutaneous or retrograde through indwelling stent</td>
<td>7 Tx grade 1–2, 2 Tx grade 3</td>
<td>56% (5 out of 9 alive and disease free; 1 dead from disease)</td>
</tr>
<tr>
<td>Jarret et al. (1995)</td>
<td>17 patients (19 units)</td>
<td>9–111 months Mean: 55 months</td>
<td>Percutaneous</td>
<td>Percutaneous</td>
<td>4 Ta grade 1, 7 Tx grade 2, 6 Tx grade 3</td>
<td>67% disease free; 33% recurrence. Cancer related mortality only in grade 3 tumors (2 patients, 12%)</td>
</tr>
<tr>
<td>Patel et al. (1998)</td>
<td>13 patients (17 units)</td>
<td>3–33 months Mean: 15 months</td>
<td>Ureteroscopic</td>
<td>Retrograde through indwelling (3) or transvesical stent (10)</td>
<td>8 Ta grade 1, 5 Ta grade 2</td>
<td>88% (15 renal units) disease free. Recurrences in grade 2 only</td>
</tr>
<tr>
<td>Clark et al. (1999)</td>
<td>17 patients (18 units)</td>
<td>1.7–75.5 months Mean: 20.5 months</td>
<td>Percutaneous</td>
<td>Percutaneous</td>
<td>15 Ta, 2 T1, 1 T2, 14 grade 1–2, 4 grade 3</td>
<td>65% (11 patients) alive and disease free</td>
</tr>
<tr>
<td>Liatkos et al. (2001)</td>
<td>30 patients</td>
<td>11 months – 14 years Mean: 49 months</td>
<td>Percutaneous</td>
<td>Percutaneous</td>
<td>Most were Ta or T1, 7 grade 1</td>
<td>14 vs 50% recurrence in untreated group (low grade). Statistically significant benefit in low grade only</td>
</tr>
<tr>
<td>Rastinehad et al. (2009)</td>
<td>50 renal units</td>
<td>61 ± 55 months</td>
<td>Percutaneous</td>
<td>Percutaneous</td>
<td>Most were Ta or T1, 27 low grade, 23 high grade</td>
<td>No statistical difference between any of the treated vs untreated groups</td>
</tr>
<tr>
<td>Giannarini et al. (2011)</td>
<td>22 renal units</td>
<td>2–237 months Median: 42 months</td>
<td>NA</td>
<td>Percutaneous</td>
<td>All Ta or T1</td>
<td>59% recurrence rate (13 out of 22)</td>
</tr>
</tbody>
</table>

**Cumulative:** 135 renal units

**Majority are Ta or T1:** More low grade than high grade

**Favorable response observed in low-grade patients**

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Bachir & Kassouf, Expert Rev Anticancer Ther 2012
AUA-2016 (PD 13-08)

• 30-yr experience with 250 pts who underwent percutaneous resection of UTUC

• No benefit with BCG or MMC instillations

• Prolong surveillance require due to delayed recurrences (>10 yrs)
Possible explanations for lack of definitive demonstrable efficacy:

- Insufficient number to show clinical significance due to relative rarity of the disease
- An inadequate delivery system
- Inadequate resection of primary disease (residual disease present)
- Retrospective bias: patients who received upper tract instillations were at higher risk (high grade, large)
- Tumor of the upper tract may have different biology
Upper tract instillations

• Performed under low pressure and absence of infection
  – Antegrade through nephrostomy tube
  – Retrograde directly into a ureteral catheter
  – Via reflux in patient with ureteral stent or iatrogenically inducing vesicoureteral reflux
Retrograde instillation via reflux

- 7Fr DJ catheter inserted
- Cystogram performed to ensure reflux and volume need for contrast to be seen in the renal pelvis
- Instillation of similar concentration of BCG or mitomycin given for 2 hrs

Patel, J Urol 1998
• Performed cystogram in patients with indwelling stents
  – Only 56% demonstrated reflux
  – Average volume needed to be instilled 170cc

Yossepowitch, J Urol 2005
Thermosensitive polymer gel Mitogel
(trial underway)
Conditional Survival After Radical Nephroureterectomy for Upper Tract Carcinoma

Guillaume Ploussard\textsuperscript{a,b}, Evangelos Xylinas\textsuperscript{c,d}, Yair Lotan\textsuperscript{c}, Giacomo Novara\textsuperscript{f}, Vitaly Margulis\textsuperscript{g}, Morgan Rouprêt\textsuperscript{g}, Kazumasa Matsumoto\textsuperscript{h}, Pierre I. Karakiewicz\textsuperscript{i}, Francesco Montorsi\textsuperscript{j}, Mezut Remzi\textsuperscript{k}, Christian Seitz\textsuperscript{k}, Douglas S. Scherr\textsuperscript{l}, Anil Kapoor\textsuperscript{m}, Adrian S. Fairey\textsuperscript{n}, Ricardo Rendon\textsuperscript{o}, Jonathan Izawa\textsuperscript{p}, Peter C. Black\textsuperscript{q}, Louis Lacombe\textsuperscript{r}, Shahrokh F. Shariat\textsuperscript{c,k}, Wassim Kassouf\textsuperscript{c,}\textsuperscript{a}

\textbf{N=3544}

\begin{itemize}
\item \textbf{<pT2N0-x}}
\item \textbf{pT2N0-x}}
\item \textbf{pT3-4N0-x}}
\item \textbf{<pT3-4N1-3}}
\item \textbf{pT3-4N1-3}}
\end{itemize}
Predictors of muscle-invasive UTUC?
• Factors associated with invasive UTUC
  • Hydronephrosis
  • Local invasion on imaging
  • Positive urine cytology
  • High grade on biopsy
  • Sessile architecture
  • Large tumor burden

Favaretto, Shariat et al, BJUI 2011
Brien J Urol 2010; Margulis, J Urol 2010
Radical Nephroureterectomy (RNU)

- **Indications:** Suspicion for infiltrating UTUC on imaging
  High-grade tumor (urine cytology or biopsy)

- **Open RNU**
  - Remains the gold standard
  - But significant morbidity

- **Open vs. Laparoscopic RNU**
  - High pressure pneumoperitoneum can lead to disseminated mets/port site recurrences?
  - Intravesical disease recurrence increased?
Laparoscopic RNU NOT inferior to open

Comparison Between Laparoscopic and Open Radical Nephroureterectomy in a Contemporary Group of Patients: Are Recurrence and Disease-Specific Survival Associated with Surgical Technique?  
Favaretto Eur Urol 2010

30% of LRN and 19% of ORN had no LN dissection

Precautions with pneumoperitoneum to avoid spillage:
1. Avoid entering urinary tract
2. Avoid direct contact instrument and tumor
3. Kidney and ureter removed en bloc with bladder cuff
4. Advanced tumors (T3/T4 and/or N+/M+) not preferred until proven otherwise

Fairey, BJUI 2013, Walton BJUI 2010
Greco BJUI 2009, Waldert BJUI 2008
Randomized Study of Open vs. Lap RNU

- 80 patients randomized: mean follow up 41 mos
- Distal ureter managed extravesically in both groups

Simone et al., Eur Urol, 56(3): 520–26, 2009

Overall Cohort

pT3  p=0.039, p=0.004

High Grade  p=0.078, p=0.014

Simone et al., Eur Urol, 56(3): 520–26, 2009
Distal Ureterectomy

- Criteria for distal ureterectomy:
  - Solitary tumor
  - Lower 1/3 of ureter
  - Stage ≤ pT2

- RNU vs. distal ureterectomy: **no difference in survival**
  - French Collaborative National Database (52 pts with segmental resection vs 416 with RNU)
  - SEER analysis (569 pts with segmental resection vs 1222 RNU)

Colin et al, BJUI, 1464: 410, 2012
Impact of Distal Ureter Management on Oncologic Outcomes Following Radical Nephroureterectomy for Upper Tract Urothelial Carcinoma

- 2681 patients
  - 68% transvesical approach
  - 29% extravesical approach
  - 3% endoscopic approach
- Median follow-up: 57 months

No difference in survival

Endoscopic approach associated with higher intravesical recurrence rates

*Kapoor, CUAJ 2014; Xylinas, et al Eur Urol 2012*
The Extent of Lymphadenectomy Seems to Be Associated with Better Survival in Patients with Nonmetastatic Upper-Tract Urothelial Carcinoma: How Many Lymph Nodes Should Be Removed?

Marco Roscigno a,*, Shahrokh F. Shariat b,†, Vitaly Margulis e, Pierre Karakiewicz m, Mesut Remzi d,

- N=552; Median FU: 48mo
- 13 centers retrospective
- Median removed LN: 5 (1-41)

pN+ (n=140)
Extent of LAD not associated with outcomes

pN0 (n=412)
Extent of LAD associated with RFS and CSS (p < 0.01)

Landing Sites for Ureteral Carcinoma

Kondo T J Urol 2007
Adjuvant chemo in pts with CompLND, IncompLND, and No-LND in 18%, 6%, and 2%

- # of nodes removed was not prognostic
Patterns of Lymphatic Metastases in Upper Tract Urothelial Carcinoma and Proposed Dissection Templates
Lymphadenectomy

- Lymphadenectomy: optimal staging therapeutic?

- No trial has shown impact on survival
Incidence of Downstaging and Complete Remission After Neoadjuvant Chemotherapy for High-Risk Upper Tract Transitional Cell Carcinoma

Surena F. Matin, MD, FACS; Vitaly Margulis, MD; Ashish Kamat, MD; Christopher G. Wood, MD; H. Barton Grossman, MD; Gordon A. Brown, DO; Colin P. N. Dinney, MD; Randall Millikan, MD, PhD; and Arlene O. Siefker-Radtke, MD

- N=107 controls
- N=43 Neoadjuvant Rx. Bx: HG UTUC

25% Reduction ≥ pT2
42% Reduction ≥ pT3
CR 14%
# Neoadjuvant Chemotherapy Improves Survival of Patients With Upper Tract Urothelial Carcinoma

Sima Porten, MD; Arlene O. Siefker-Radtke, MD; Lianchun Xiao, MS; Vitaly Margulis, MD; Ashish M. Kamat, MD; Christopher G. Wood, MD; Eric Jonasch, MD; Colin P. N. Dinney, MD; and Surena F. Matin, MD

## TABLE 3. Multivariate Cox Model for 5-Year Overall Survival and Disease-Specific Survival

<table>
<thead>
<tr>
<th>Variable</th>
<th>HR (95% CI)</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Overall survival</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Age</td>
<td>1.02 (0.998-1.05)</td>
<td>.075</td>
</tr>
<tr>
<td>Neoadjuvant chemotherapy</td>
<td>0.42 (0.19-0.94)</td>
<td>.035</td>
</tr>
<tr>
<td>$\geq 8$ Lymph nodes removed</td>
<td>0.75 (0.40-1.40)</td>
<td>.370</td>
</tr>
<tr>
<td>Sessile tumor architecture</td>
<td>1.16 (0.69-1.96)</td>
<td>.580</td>
</tr>
<tr>
<td>Disease-specific survival</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Age</td>
<td>1.01 (0.98-1.04)</td>
<td>.560</td>
</tr>
<tr>
<td>Neoadjuvant chemotherapy</td>
<td>0.19 (0.06-0.61)</td>
<td>.006</td>
</tr>
<tr>
<td>$\geq 8$ Lymph nodes removed</td>
<td>0.54 (0.24-1.23)</td>
<td>.140</td>
</tr>
<tr>
<td>Sessile tumor architecture</td>
<td>2.77 (1.30-5.89)</td>
<td>.008</td>
</tr>
</tbody>
</table>

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*Cancer 2014*
In considering neoadjuvant chemotherapy, the following factors help in counseling pts:

- Biopsy grade (high grade 66% PPV for higher stage)
- Visual appearance of the tumor (sessile)
- Large tumor burden
- Local invasion on radiographic studies (parenchymal, renal sinus fat, periureteral)
- High grade hydronephrosis
- Adequate renal function for cisplatin-based regimens

Pts with hilar/regional adenopathy should be treated with upfront chemotherapy
Accurate staging influences therapeutic decision →
RNU vs endoscopy, Lymphadenectomy, Neoadjuvant Chemotherapy

<table>
<thead>
<tr>
<th>Variables</th>
<th>Muscle Invasive</th>
<th>Nonorgan Confined</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>HR (95% CI) p Value</td>
<td>HR (95% CI) p Value</td>
</tr>
<tr>
<td>Ipsilat hydronephrosis</td>
<td>12.0 (5.1–28.2) &lt;0.001</td>
<td>5.1 (2.3–11.5) &lt;0.001</td>
</tr>
<tr>
<td>High grade URS biopsy</td>
<td>4.5 (1.9–10.4) &lt;0.001</td>
<td>3.9 (1.8–8.7) &lt;0.001</td>
</tr>
<tr>
<td>Pos urinary cytology</td>
<td>2.3 (0.8–7.0) 0.172</td>
<td>3.1 (1.0–10.0) 0.035</td>
</tr>
<tr>
<td>Tumor site</td>
<td>1.7 (1.0–2.8) 0.055</td>
<td>1.5 (0.9–2.4) 0.133</td>
</tr>
<tr>
<td>Gender</td>
<td>1.3 (0.6–2.9) 0.52</td>
<td>1.4 (0.6–3.0) 0.47</td>
</tr>
<tr>
<td>Age</td>
<td>1.0 (1.0–1.1) 0.80</td>
<td>1.0 (1.0–1.1) 0.91</td>
</tr>
</tbody>
</table>

**Muscle invasion**
- PPV 24%, 46%, 89%
- NPV 100%
- Hydro, Cyto+, HG
- No Hydro, Cyto-, LG

**Non-organ confined UTUC**
- PPV 14%, 35%, 73%
- NPV 100%
- Hydro, Cyto+, HG
- No Hydro, Cyto-, LG

Brien J Urol 2010
Postoperative Nomogram for Relapse-Free Survival in Patients with High Grade Upper Tract Urothelial Carcinoma


Points

| Points | 0 | 5 | 10 | 15 | 20 | 25 | 30 | 35 | 40 | 45 | 50 | 55 | 60 | 65 | 70 | 75 | 80 | 85 | 90 | 95 |

pT stage

| T0 | T1 | T2 | T3 |

pN stage

| N0 | N1 | N2 | N3 |

Age at diagnosis

| 98 | 90 | 60 | 40 |

Architecture

| papillary | sessile |

Total points

| 0 | 10 | 20 | 30 | 40 | 50 | 60 | 70 | 80 | 90 | 100 | 110 | 120 | 130 | 140 | 150 | 160 | 170 | 180 |

Overall probability for relapse

| 0.05 | 0.1 | 0.2 | 0.3 | 0.4 | 0.5 | 0.6 | 0.7 | 0.8 | 0.9 |

Risk stratification

- low-risk
- intermediate-risk
- high-risk
- very high-risk

Relapse-free Survival Rate

1-yr: 97.5% (95.0-98.6)
2-yr: 94.7% (91.3-96.7)
5-yr: 88.6% (83.6-96.7)
3-yr: 66.6% (83.3-89.3)
4-yr: 64.1% (57.3-70.1)
5-yr: 40.3% (32.0-48.3)
6-yr: 23.8% (16.7-31.6)
7-yr: 12.5% (6.6-20.7)

76% Accuracy
Other prognostic factors following nephroureterectomy

• Extranodal extension
• Tumor location and multifocality
• Lymphovascular invasion

Fajkovic, J Urol 2012
Yafi, BJUI 2012; Chromecki, Eur Urol 2012
Novarra, Eur Urol 2010, Kikuchi, JCO 2009
Adjuvant chemo:

- Pooled analysis of 482 pts receiving AC and 1300 without AC
• 171 pts with pT3N0 treated with nephro-u
  • Adjuvant cisplatin-based chemotherapy associated with improved survival in pT3-4N+ on MVA

J Urol 2015
• 229 pts with pT3/4 or N treated with nephro-u
  • Adjuvant MVAC chemotherapy associated with improved survival in patients compared to adjuvant GC or no adjuvant chemo

J Urol 2015
## Canadian multicenter experience (n=1029)

### Pre-operative and post-operative estimation of renal function

<table>
<thead>
<tr>
<th></th>
<th>All patients</th>
<th>High-risk patients*</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Pre-operatively</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Median eGFR (IQR)</td>
<td>58.8 (55.7-61.1)</td>
<td>58.6 (56.3-60.9)</td>
</tr>
<tr>
<td>Eligible for cisplatin-based therapy</td>
<td>359 (49%)</td>
<td>105 (48%)</td>
</tr>
<tr>
<td>Ineligible for cisplatin based therapy</td>
<td>379 (51%)</td>
<td>112 (52%)</td>
</tr>
<tr>
<td><strong>Post-operatively</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Median eGFR (IQR)</td>
<td>46.6 (43.3-49.0)</td>
<td>47.3 (44.8-49.0)</td>
</tr>
<tr>
<td>Eligible for cisplatin-based therapy</td>
<td>94 (18%)</td>
<td>34 (21%)</td>
</tr>
<tr>
<td><strong>Ineligible for cisplatin based therapy</strong></td>
<td>431 (82%)</td>
<td>126 (79%)</td>
</tr>
</tbody>
</table>

75% of patients who received adjuvant chemotherapy had eGFR <60

Lane, Cancer 2010
Yafi, Urol Oncol 2013
Adjuvant Chemotherapy

• Platinum-based chemotherapy expected similar results to bladder urothelial carcinoma
  – POUT trial is underway
  – Adjuvant PD-L1 therapy trial on going

• Adjuvant chemotherapy
  – Only for select patients due to comorbidities and poor renal function
  – Impact on survival is unclear
    – lack of efficacy of AC versus use of suboptimal regimen/dose because of poor renal function
Role of postoperative intravesical instillation of chemotherapy?

• RCT of 284 pts
• MMC vs standard
• Endpoint: bladder recurrence
  • 1-yr 16% vs 27% (p=0.03)
  • Biopsy not mandated
  • MMC given 7-10d postop

O’ Brien, Eur Urol 2011
• RCT of 77 pts
• THP vs saline (30min)
• Endpoint: bladder recurrence
  • 2-yr 17% vs 42% (p=0.025)
  • Biopsy mandated
  • THP given 48hr postop

• ?post-ureteroscopic resection
EUA 2016

<table>
<thead>
<tr>
<th>After RNU, $\geq 5$ years</th>
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<td><strong>Non-invasive tumour</strong></td>
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<td>• Cystoscopy/urinary cytology at 3 months and then yearly.</td>
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<td>• CT every year</td>
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<td><strong>Invasive tumour</strong></td>
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<td>• CT urography every 6 months over 2 years and then yearly.</td>
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<td><strong>After conservative management, $\geq 5$ years</strong></td>
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<td>• Urinary cytology and CTU at 3 and 6 months, and then yearly.</td>
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<td>• Cystoscopy, ureteroscopy and cytology <em>in situ</em> at 3 and 6 months, and then every 6 months over 2 years, and then yearly.</td>
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Canadian guidelines for postoperative surveillance of upper urinary tract urothelial carcinoma

Anil Kapoor, MD, FRCSC; Christopher B. Allard, MD; Peter Black, MD, FRCSC; Wassim Kassouf, MD, FRCSC; Christopher Morash, MD, FRCSC; Ricardo Rendon, MD, FRCSC

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UTUC: upper urinary tract urothelial carcinoma; LG: low grade; HG: high grade; Hx: history; PE: physical examination; CXR: chest x-ray; CTU: computed tomography urography; pT<2 includes pTis, pTa and pT1; *ipsilateral ureteroscopy with selective cytology or biopsy should be performed following nephron-sparing procedures.
Conclusions- Current Standards

- Elective nephron-sparing therapies have gained acceptance in patients with low volume/low grade disease
- RNU is gold standard for high grade renal pelvis/upper ureteral tumors
  - Distal ureterectomy valid option for unifocal distal ureteral lesions
  - Lap/robotic RNU acceptable techniques
- Complete excision of bladder cuff mandatory
  - Endoscopic approaches possibly inferior
- Cystoscopic surveillance of the bladder is mandatory following therapy for UUTC
Conclusions- Current Controversies

- Role of NBI/fluorescence unclear
- Benefit and route of administration of intracavitary instillations unclear
  - Appears to work best for CIS
- Post-RNU intravesical chemotherapy (i.e., MMC)
- Therapeutic benefit of lymphadenectomy for UUTC remains unclear
- Neoadjuvant chemotherapy for high risk disease
  - Less controversial for LN positive (definitive chemotherapy)
- Adjuvant chemotherapy questionable role