Advancements in the Treatment of Upper Tract Urothelial Carcinoma

Angela Smith, MD
Assistant Professor of Urology
Outline

• Diagnostic Testing
  – Imaging, endoscopy
  – New technologies

• Treatment Strategies
  – Endoscopic management
  – Topical treatment
  – Chemotherapy
  – Surgical management
  – Role of lymph node dissection
  – Postoperative care
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 2011; Chromecki, Shariat et al., Nature Rev 2011
Increasing Attention to UTUC

- Gaining more widespread interest
- SUO supported the first symposium devoted solely to UTUC in 2012 – standing room only
- BCAN established an UTUC working group in 2013
- AUA devoted time in the plenary session and educational courses
- Societe Internationale d’Urologie supported International Consultation on Urological Diseases on UTUC
Urothelial Carcinoma of the Bladder and the Upper Tract Embryology

**Bladder:** UG sinus (endoderm)
**Trigone:** mesonephros (mesoderm)
**Ureter:** mesonephros (mesoderm)

Green et al, JU 2013
Urothelial carcinoma of bladder and upper tract: **DISPARATE TWINS**

<table>
<thead>
<tr>
<th></th>
<th>Bladder UC</th>
<th>Upper tract UC</th>
</tr>
</thead>
<tbody>
<tr>
<td>No. randomized trials</td>
<td>238</td>
<td>3</td>
</tr>
<tr>
<td>Gender</td>
<td>4:1 incidence</td>
<td>2:1 incidence</td>
</tr>
<tr>
<td></td>
<td>Delay dx &amp; worse outcomes</td>
<td>No effect on stage &amp; outcomes</td>
</tr>
<tr>
<td>Aristolochic acid</td>
<td>Very minor role</td>
<td>Aristolactam-DNA adducts (Taiwan &amp; Balkan)</td>
</tr>
<tr>
<td>Microsatellite instability</td>
<td>Minor role</td>
<td>HNPCC, mismatch repair genes</td>
</tr>
<tr>
<td>Impact of stage on outcomes</td>
<td>≤pT1 worse</td>
<td>pT4 worse</td>
</tr>
<tr>
<td>Intracavitary therapy</td>
<td>Essential in management</td>
<td>Anatomical barriers</td>
</tr>
<tr>
<td>Lymphadenectomy</td>
<td>Important &amp; templates known</td>
<td>Role &amp; templates unknown</td>
</tr>
<tr>
<td>Perioperative chemotherapy</td>
<td>Level 1 evidence</td>
<td>Post-op decrease in eGFR</td>
</tr>
</tbody>
</table>

Bladder UC and UTUC share many features but **distinct diseases**: 
- Practical, anatomical, biological, and molecular differences that warrant consideration in clinical decision-making

Green, Shariat et al., J Urol 189: 1214-21, 2013
Diagnostic Testing
Imaging

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

<table>
<thead>
<tr>
<th>Size</th>
<th>Sensitivity</th>
<th>Specificity</th>
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</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
    (eGFR<30) → nephrogenic systemic fibrosis

Roupret Eur Urol 2011, Chromecki, Shariat Nat Rev 2011
Cystoscopy & Cytology

• Cystoscopy: mandatory
• Positive urine cytology suggestive of UTUC if cysto negative & no CIS bladder or prostatic urethra
• Cytology *not as good for UTUC* as it is for bladder cancer
• Positive cytology suggestive of high grade/invasive UTUC

*Roupret Eur Urol 2011, Chromecki, Shariat Nat Rev 2011*
Diagnostic Ureteroscopy

• Ureteroscopy: diagnosis, aspect of tumor, biopsy, determine grade in 90%
• Useful for diagnostic uncertainty, when conservative management considered, or in patients with solitary kidney

Roupret Eur Urol 2011
Chromecki, Shariat Nat Rev 2011
New Technologies

- Access, laser, baskets, biopsy forceps
- Digital ureteroscopes
- Narrow band imaging (NBI)
- Fluorescence
- Endoluminal Ultrasound
Flat Wire Basket for Papillary Tumors
Other Tools

- Cold cup biopsy forceps (Piranha)

- Use of **access sheath** facilitates multiple biopsies, yielding 88.6% grade concordance

Gorin MA Urol 2011
NBI : Narrow Band Imaging

• Two discrete bands:
  – Blue at 415nm displays superficial capillary networks in brown
  – Green at 540nm displays subepithelial vessels in cyan
  – When combined: high contrast image of epithelial and subepithelial surface
Fluorescence (hexaminolevulinate)

- FDA approved for bladder
- Minimal experience in upper tract
- Theoretically can aid in identification of small tumors, surveillance after endoscopic therapy
Possible Role of High Frequency Endoluminal Ultrasound for Better Staging of UTUC

- Mechanically rotating transducer in ~5Fr probe—multiple configurations
- Passed over wire after initial ureteroscopy
- Same processor as used in Pulmonary and GI
- Axial US image
- 20 Mhz frequency in B-mode
- Depth range 1-6 cm, best images at 2-3cm
ELUS: Case Example

- 84 yo, high grade, possible T1 on biopsy
- CT: ‘no suggestion of invasion’
- ELUS: clearcut invasion

- Path: ypT2 N0

*Case courtesy of Surena Matin*
Initial Experience with ELUS: Pathologic Correlation in a Pilot Study

- 15 patients
- 7 underwent primary nephroureterectomy allowing pathologic validation
- Prediction of invasive disease (n=7)
  - PPV= 66.7%
  - NPV= 100%
  - Pilot data that needs to be validated
- Current grant-funded study allowing for blinded evaluation by 2 Radiologists, ongoing (61 ELUS, 23 evaluable)
60 yo with 3 cm distal ureteral mass

• Papillary tumor on a stalk
• No other tumors above or below
• Biopsy = low grade
• eGFR= 45
60 yo with 3 cm LG distal ureteral mass, GFR = 45

Treatment Choice?

1. Endoscopic ablation alone
2. Endoscopic ablation with BCG
3. Endoscopic ablation with MMC
4. Distal ureterectomy with reimplant
5. Nephroureterectomy
Conservative Management

- Endoscopic therapy
- Role of rebiopsy
- Role of topical therapy
Endoscopic Management of UTUC

- Traditionally reserved for solitary kidneys and high risk patients
- Increasingly accepted as primary definitive therapy in those with low grade, minimal volume disease
- Can have significant local recurrence rate
- Requires more stringent local follow up
- Ideal candidates:
  - Single small low-grade tumor

Krambeck A et al J Urol 2007; Giannarini 2011
Accuracy of URS Biopsy

- Evaluated accuracy of URS biopsy to predict stage and grade of disease in 40 patients undergoing NUx
- Compared clinical to pathologic stage and grade
  - 31/40 (78%) had matching clinical and pathologic grades
  - 9/40 (22%) up-graded
  - 45% pathologic “upstaging” based on clinical biopsy stage

<table>
<thead>
<tr>
<th>Surgical Stage</th>
<th>No. Biopsy Stage Ta</th>
<th>No. Biopsy Stage T1+</th>
</tr>
</thead>
<tbody>
<tr>
<td>pTa</td>
<td>12</td>
<td>0</td>
</tr>
<tr>
<td>pT1–pT3</td>
<td>10*</td>
<td>5</td>
</tr>
<tr>
<td>Totals</td>
<td>22</td>
<td>5</td>
</tr>
</tbody>
</table>

Guarnizo E et al, J Urol 163:52 2000
Re-biopsy of upper tract lesions

• Initial biopsy, then re-biopsy in 6 weeks\(^1\)
  – Increase in grade in 18/65 cases (28%)
  – Increase in stage in 21/65 cases (32%)
  – Reclassified LG to HG in 24/56 (43%)

• Post-cystectomy with UTUC\(^2-4\)
  – High stage UT disease more common
  – Poorer survival than de novo UT disease

\(^1\) Smith AK, et al *Urology* 78:82-86, 2011; \(^2\) Balaji KC *J Urol* 162:1603-6, 1999
Questions from Both Studies

• How was clinical staging done?
  – Very difficult to do accurately
  – Definition significantly alters conclusion about “upstaging”

• What was the influence of tumor size or volume (sampling bias)?
Influence of Tumor Size and Limitations of Clinical Staging on URS Accuracy

- 66 patients with URS biopsy undergoing nephroureterectomy by single surgeon
- Tumor size was assessed from pathology evaluation by single dimension, surface area (cm²), volume (cm³)
- “cTx” assigned when no indication of presence or degree of invasion on biopsy or imaging

Porten S et al, SUO abstract, 2013
Influence of Tumor Size on Accuracy of Biopsy
N=66 patients

Clinical stage allocation

<table>
<thead>
<tr>
<th>Source</th>
<th>Pathologic description or imaging findings</th>
<th>Classification</th>
</tr>
</thead>
<tbody>
<tr>
<td>Biopsy and imaging</td>
<td>Invasion cannot be assessed; or, no comment made regarding invasiveness or its absence</td>
<td>cTx</td>
</tr>
</tbody>
</table>

Tumor size characteristics predictive of upstaging (pT2+) in patients with clinical stage Tx (N=30)

<table>
<thead>
<tr>
<th>Tumor size parameter</th>
<th>&lt;pT2 (N=18)</th>
<th>pT2+ (N=12)</th>
<th>Fisher's exact test P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Tumor length</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>&lt;=3.8</td>
<td>9(50%)</td>
<td>1(8.3%)</td>
<td>0.0235</td>
</tr>
<tr>
<td>&gt;3.8</td>
<td>9(50%)</td>
<td>11(91.7%)</td>
<td></td>
</tr>
<tr>
<td>Surface area (cm²)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>&lt;=8.4</td>
<td>9(50%)</td>
<td>4(33.3%)</td>
<td>0.4651</td>
</tr>
<tr>
<td>&gt;8.4</td>
<td>9(50%)</td>
<td>8(66.7%)</td>
<td></td>
</tr>
<tr>
<td>Tumor Volume (cm³)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>&lt;=12.2</td>
<td>8(53.3%)</td>
<td>3(27.3%)</td>
<td>0.2463</td>
</tr>
<tr>
<td>&gt;12.2</td>
<td>7(46.7%)</td>
<td>8(72.7%)</td>
<td></td>
</tr>
<tr>
<td>Aggregate Volume (cm³)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>&lt;=13.3</td>
<td>8(53.3%)</td>
<td>3(27.3%)</td>
<td>0.2463</td>
</tr>
<tr>
<td>&gt;13.3</td>
<td>7(46.7%)</td>
<td>8(72.7%)</td>
<td></td>
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3 cm distal ureteral mass

- Low grade Ta completely resected
- Adjuvant topical therapy?
Topical Therapy

• Role is not firmly established
• Recent systematic review only identified 19 studies reporting outcomes
• Most established is BCG, although a significant advantage has yet to be proven

BCG for Curative Intent

- 11 studies evaluated the role of BCG as curative therapy for UUT CIS
- Sample sizes small
  - n=5-11 in most
  - One “larger” study by Giannarini (n=55)
- 6 week induction course only, perc NT
- Recurrence rates 10-54% (overall 32%)

• Retrospective study n=55 (64 RUs)
• Median follow-up 3.5 years
• Negatively selected patients
• Results
  – CIS: 40% recurred (5% progressed)
  – Ta/T1: 59% recurred (41% progressed)
  – Eventual Nux in 11% (5% CIS, 23% Ta/T1)
  – Mostly minor adverse events (20%)
BCG with Adjuvant Intent

- After resection of papillary UUT-UCC
- 7 studies
- Sample sizes range (most ~20)
  - Largest study Rastinehad, n=50 (89 RUs)
- All six week induction courses, perc NT
- Recurrence in 5-59% (overall 30%)

Mitomycin C with Adjuvant Intent

- 3 retrospective studies
- Sample sizes ranged n=13 to n=32
- One 3 week course, 2 studies with 6 week course
- Instilled via ureteral catheter
- Recurrences
  - G1: n=14 (21%)
  - G2: n=12 (42%)
  - G3: n=5 (20%)

Mitomycin C instillation following ureterorenoscopic laser ablation of upper urinary tract carcinoma

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¹Wales Deanery, Department Urology, Cardiff, UK and Islamic University of Gaza, College of Medicine, Gaza, Palestine, ²Southampton University Hospitals NHS Trust, Southampton, ³Department of Urology, Ninewells Hospital and Medical School, Dundee, UK

• Prospective study between 2005-2011, 20 renal units (19 patients)
  • G1Ta (n=2)
  • G2Ta (n=14)
  • G3Ta (n=2)
  • G3T1 (n=2)
• 40mg/40mL MMC instilled 1mL/min
• Ureteral catheter clamped x 20 min
• Mean follow-up 24 months
  • 35% (n=7) with recurrences
  • 15% (n=3) with strictures
  • No systemic side effects or renal decline

CASE:
69yo M with HG UTUC

• 1 cm left mid-ureteral lesion
• HGT1, no muscle present
• No obvious invasion on CT
• GFR 60
• HTN, DM2 (controlled)
• Desires definitive management
69yo M w/ 1cm mid-ureteral HG UTUC, GFR 60

What is your treatment choice?

1. Segmental ureterectomy
2. Neoadjuvant chemo + Nux
3. Neoadjuvant chemo + Nux + LND
4. Nux
5. Nux + LND
Chemotherapy
CKD in UTUC Population

• The majority of our patients have underlying CKD…
  – Age related loss of renal function
  – Tobacco-related comorbidities/vasculopathy
  – 52% of patients presenting with UTUC have eGFR<60 mL/min/1.73m$^2$

• …which worsens after nephroureterectomy
  – NU may eliminate chemo as an option in 49% of high-risk patients if it is deferred to the adjuvant setting
Neoadjuvant Chemotherapy Regimens

- DD MVAC + bevacizumab
- Paclitaxel/Carboplatin
- MVAC
- GC
- CISCA
- Ongoing trials evaluating GC and GCa
Neoadjuvant Chemotherapy

- Pathologic downstaging/CR
  - Matched historical cohort
  - Downstaging ~45%, CR 14%

![Disease stages in patients who received neoadjuvant chemotherapy and patients undergoing initial surgery](image)

- Pathologic Stage Classification

Matin Cancer 2010
Neoadjuvant Chemotherapy: 5-year Survival

Porten S, Cancer 2014
What About Adjuvant Chemotherapy?

- 145 patients with pT3-4 or pN+ treated with nephroureterectomy
  - Adjuvant chemotherapy was not associated with improved survival
    
    Vassilakopoulou, Cancer 2011

- 542 patients with pT3-4 or pN+ treated with nephro-u
  - Adjuvant chemotherapy was not associated with improved survival
    
    Hellenthal, J Urol 2009
Chemotherapy: Bottom Line

• All patients with high-grade UTUC should be considered for NAC
• Eligible patients with >pT3 should be considered for adjuvant chemotherapy
  – If ineligible, consider adjuvant clinical trials
Surgical Therapy

- Role of Lymphadenectomy?
- Nephroureterectomy
  - Kidney, ureter, bladder cuff
  - Open → Laparoscopic → Robotic
- Distal/segmental ureterectomy
  - Psoas hitch, Boari flap, renal mobilization
- Partial nephrectomy
  - Extremely narrow indication
Nephroureterectomy: Nuances

- Adrenal can be safely preserved in most all cases except suspected T4 disease
- Ureteral tumors: Don’t strip ureter, keep copious periureteral tissue
- Clip ureter after hilar control
- Complete DU/BC excision \textit{demands} visual intraoperative confirmation
Robotic Nephroureterectomy: UNC Experience

- Last 2.5 years, n= 26 consecutive RANUs
- Mean perioperative outcomes
  - OR time ~4 hours, 15 minutes
  - EBL 217mL
  - Length of stay 2 days
- Single docking technique in 62%
- Pathology: 68% high grade, 32% low grade
- Complications (n=4):
  - 2 bladder leaks
  - 1 Bleed
  - 1 Postop delirium
- Recurrences:
  - Bladder (n=4)
  - Retroperitoneal (n=1)
  - Distant metastases (n=1)
Robotic Nephroureterectomy and RPLND without repositioning

• VIDEO

HEAD

[Image of a medical procedure with markings and instruments]
Distal Ureter and Bladder Cuff

- Transurethral incision of UO is associated with higher risk of bladder tumor recurrence (n=208)\(^1\)
- Stapling also w higher risk of PSM\(^2\)
- If it was easy, you probably didn’t get it all

\(^1\)Chiang PH J Endou 2011
\(^2\)Matin SF and Gill IS 2004
Distal Ureter and Bladder Cuff

- Lateral ‘extravesical’ approach requires:
  - Division of entire lateral pedicle of bladder
  - Visually confirm resection of UO/cuff by opening bladder around cuff (no need for separate cystotomy or clamshell)

- Exception: invasive distal ureteral tumors
  - Probably best removed by separate cystotomy, possible partial cystectomy
**Curative Role for Lymphadenectomy?**

**FIG. 1.** Kaplan-Meier CSS curves by pN status; there were significant differences in survival among the pN0, pNx and pN+ groups.

**FIG. 3.** Kaplan-Meier CSS curves for patients with 1–5, 6–10 or ≥11 LNs removed in ≥pT3 disease.
Primary site of lymph node metastases in UTUC

Adapted from data in Kondo T et al 2007
Is LND Therapeutic?

Fig. 3. Patient survival improved when number of LNs removed increased but there was no statistical significance. Values above curves indicate number of lymph nodes removed.
Lymph Node Count

- Roscigno et al, 2008
  - n=132, LND = 95
  - Number of LNs found to be independent predictor of:
    - DFS (HR 0.93 p = .03)
    - CSS (HR 0.90, p=.007)
RPLND/PLND: Patient Selection

- Nodal disease closely linked to stage, but clinical staging is difficult …
- Thus:
  - High grade tumor
  - Sessile architecture
  - Large tumor (sampling bias from bx)
  - By definition, those receiving NAC
Lymph Node Dissection

• VIDEO
CASE: 69yo M with HG UTUC

- Patient has successful robotic nephroureterectomy with lymph node dissection
- Pathology pT2N0 urothelial cancer, negative margins
- What surveillance regimen would you choose?
What surveillance regimen would you choose?

1. Postop MMC, local cysto q3mos, CTU in 1 yr
2. Local cysto q3 mos, CTU in 1 yr
3. Postop MMC, local cysto q3 mos, URS in 1 yr
4. Local cysto q3 mos, URS in 1 yr
5. Local cysto q3 mos, follow with cytology only
Prevention of Bladder Tumors after Nephroureterectomy

- Prospective randomized trial of single dose MMC (ODMIT-C Trial)
  - N=105 (of 144) MMC at variable times postop
  - N=140 “standard of care”
  - Follow-up 12 months w/ cystos
- 11% absolute risk reduction
- 40% relative risk reduction
- NNT = 9
- No SAE

O’Brien T et al Eur Urol 2011
Summary

• UTUC with similarities & differences to bladder cancer
• New techniques in diagnosis and treatment with hope to improve recurrence & survival
  – Ureteroscopic techniques
  – Diagnostic modalities
  – Nephroureterectomy techniques
  – Lymph node dissection
  – Adjuvant intravesical therapy
Thank You!

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