Urothelial Tumors of the Upper Tract: Diagnosis and Management

Daniel Rapoport
April 11, 2007
Urology Grand Rounds
Overview

• Background
  – Epidemiology and risk factors
  – Natural history and prognostic factors
• Diagnosis
  – Current imaging modalities
  – Role of endoscopy and biopsy
• Management
  – Laparoscopic nephroureterectomy
  – Nephron-sparing
  – Endoscopic management

Preface

<table>
<thead>
<tr>
<th>Level of Evidence</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ia</td>
<td>Evidence from meta-analysis of randomised controlled trials</td>
</tr>
<tr>
<td>Ib</td>
<td>Evidence from at least one randomised controlled trial</td>
</tr>
<tr>
<td>Ii</td>
<td>Evidence from at least one controlled study without randomisation</td>
</tr>
<tr>
<td>Iii</td>
<td>Evidence from at least one other type of quasi-experimental study</td>
</tr>
<tr>
<td>III</td>
<td>Evidence from non-experimental descriptive studies, such as comparative studies, correlation studies, and case-control studies</td>
</tr>
<tr>
<td>IV</td>
<td>Evidence from expert committee reports, opinions or clinical experience of respected authorities, or both</td>
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<table>
<thead>
<tr>
<th>Strength of Recommendation</th>
<th>Description</th>
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<tbody>
<tr>
<td>A</td>
<td>Directly based on category I evidence</td>
</tr>
<tr>
<td>B</td>
<td>Directly based on category II evidence or extrapolated recommendation from category I evidence</td>
</tr>
<tr>
<td>C</td>
<td>Directly based on category III evidence or extrapolated recommendation from category I or II evidence</td>
</tr>
<tr>
<td>D</td>
<td>Directly based on category IV evidence or extrapolated recommendation from category I, II or III evidence</td>
</tr>
</tbody>
</table>
Epidemiology

- 5%
  - Of all renal tumors
  - Of all urothelial tumors

- 40% of renal tumors in Balkan countries
Epidemiology

- Rare: 1/100,000 incidence
- Mean: 65 yrs
- Males 2x more than females
- Caucasians 2x more than African Americans

Risk Factors

- Smoking (RR 3)
- Coffee (RR 1.3)
- Analgesics
  - Phenacetin
  - Caffeine, codeine, acetaminophen, ASA preparations
- Occupational/Environmental
  - Chemical, petroleum and plastics (RR 4)
  - Coal (RR 4)
  - Asphalt and tar (RR 5.5)
  - Blackfoot disease (Taiwan)
- Chronic Inflammation
- Chemotherapy
  - Cyclophosphamide
- Heredity
  - Balkan nephropathy
  - Lynch syndrome II (colonic tumors + other tumors)
Previous Bladder Cancer

• 80% preceded by bladder cancer *

• 2-4% incidence of metachronous upper tract tumors in superficial bladder TCC
  – Median time to recurrence approx. 70 months

• Incidence increases with time**
  – 2.7% 5-10 yrs, 8.1% 10-15 yrs

*Holmang & Johansson, 2004
** Shinka et al, 2001

Previous Bladder Cancer

• Risk factors for upper tract recurrence*
  – CIS (up to 21% risk)**
  – Stage & grade
  – Multifocal
  – Recurrent
  – (Tumor close to UO)
  – (VUR)

*Holmang & Johansson, 2004
** Rabbani et al, 2001
Upper Tract Screening in Bladder Cancer

- Low-Risk: TaG1
  - Image for hematuria
- Moderate-Risk: > 3cm, multifocal, recurrent
  - Image for hematuria or recurrence

**Best imaging modality for surveillance?**

- High-Risk: any G3, G1G, invasive
  - Annual imaging x 2 then longer

Previous Bladder Cancer

- Better prognosis than primary upper tract TCC*
- Detection bias?

Rabbani et al. 2001
Primary Upper Tract TCC Natural History

• Muscle invasive disease common
  – 40% more than bladder TCC*
  – 50-60% of renal pelvis and ureteric tumors invasive*

• 19% present with metastatic disease

Stewart et al. 2005

Propensity to Invade

• Ureter > Renal pelvis
  – Parenchyma acts as barrier
Recurrence

• Common after local therapy
  – 30-55% ipsilateral recurrence after endoscopic resection
  – 30-75% recurrence in retained stump
• Recurrence almost always distal to primary
• Contralateral upper tract tumor rare

• 2 theories: field change vs seeding

Metachronous Bladder TCC

• 20-75% incidence
• Most within 2 yrs
• NEED SURVEILLANCE

• Risk Factors:
  – Multifocal tumor
  – Pathologic tumor stage
  – Tumor size
  – Surgical modality
Prognosis
Stage most important outcome determinant
(Open Nephroureterectomy results)

<table>
<thead>
<tr>
<th>Stage</th>
<th>5 yr CSS</th>
</tr>
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<tbody>
<tr>
<td>Ta, 1, CIS</td>
<td>60-90%</td>
</tr>
<tr>
<td>T 2</td>
<td>40-75%</td>
</tr>
<tr>
<td>T 3</td>
<td>16-33%</td>
</tr>
<tr>
<td>T 4</td>
<td>0-5%</td>
</tr>
<tr>
<td>N+</td>
<td>0-4%</td>
</tr>
<tr>
<td>M+</td>
<td>0%</td>
</tr>
</tbody>
</table>

NCI SEER data; Based on pathologic stage
Munoz & Ellison, J Urol 2000
Tumor Location

• Renal Pelvis 55%
• Ureter
  – Proximal 5%
  – Mid 25%
  – Distal 70%

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THE IMPACT OF TUMOR LOCATION ON PROGNOSIS OF TRANSITIONAL CELL CARCINOMA OF THE UPPER URINARY TRACT
SUNGCHAN PARK, BUMSEOK BONG, CHOUNG-SOO KIM and HANGJONG AHN
From the Department of Urology, University of Ulsan College of Medicine, Asan Medical Center, Seoul, Korea

Table 1. Clinicopathological characteristics of 80 patients with upper tract TCC

<table>
<thead>
<tr>
<th>Grade</th>
<th>No. Pelvis</th>
<th>No. Ureter</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>4</td>
<td>2</td>
</tr>
<tr>
<td>2</td>
<td>25</td>
<td>18</td>
</tr>
<tr>
<td>3</td>
<td>15</td>
<td>23</td>
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<table>
<thead>
<tr>
<th>Pos. Dukes stage</th>
<th>No. Pelvis</th>
<th>No. Ureter</th>
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<tbody>
<tr>
<td>A</td>
<td>2</td>
<td>9</td>
</tr>
<tr>
<td>B</td>
<td>5</td>
<td>11</td>
</tr>
<tr>
<td>C</td>
<td>4</td>
<td>7</td>
</tr>
<tr>
<td>D</td>
<td>0</td>
<td>3</td>
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<tr>
<td>Radiotherapy</td>
<td>1</td>
<td>1</td>
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<table>
<thead>
<tr>
<th>Recurrence</th>
<th>No. Pelvis</th>
<th>No. Ureter</th>
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<tbody>
<tr>
<td>Local recurrence</td>
<td>2</td>
<td>12</td>
</tr>
<tr>
<td>Distant metastasis</td>
<td>5</td>
<td>6</td>
</tr>
<tr>
<td>Bladder recurrence</td>
<td>22</td>
<td>13</td>
</tr>
</tbody>
</table>
Location and Prognosis

- Renal pelvis tumor better prognosis
- Parenchyma acts as barrier to spread

![Graph showing survival rates](image)

97% vs 65% disease-specific survival at 5 yrs

Other Prognostic Factors

- Sex & Race
  - worse outcomes in Female and African-Amer.
- Histology
  - Vascular invasion correlates with mets
- Molecular Markers
  - P53, 9p21, ploidy, telomerase
Background
Diagnosis

Signs and Symptoms

- History & Physical
- Urinalysis 30%
- Asymptomatic 15%
- Imaging
  - IVP, CT, RPG
- Cystoscopy
- Ureteroscopy & Biopsy
Upper Tract Cytology

- Sensitivity related to tumor grade
  - 75% for grade 3
- Barbotage/washing most accurate
  - Releases loosely adherent cells
- False positives
  - Anything causing inflammation/infection
- Isolated positive cytology
  - May signify CIS, treatment controversial

Imaging

- IVP traditionally used
- Replaced by CT
CT Urography

- Sensitivity approaches 100%
- Specificity 60%
- Staging accuracy 60%
- Easier to perform

Disadvantages:
- may miss lesions < 5mm
- Radiation exposure

Suggestive Features

- Filling defect
- Nonvisualization
- Hydronephrosis
  - Associated with invasive TCC in 80%*
- Density
  - 10-70 HU (soft tissue)
Retrograde Pyelography

- May be useful for equivocal lesions
- Can be combined with ureteroscopy
Ureteroscopy

- Gold standard for evaluation of filling defects and obstruction

  Increases diagnostic accuracy to 85-90%

Technical Points

- Washings before biopsy of suspicious lesions
- Biopsy & ablation of base
- Do not “go deep”
  - Grade α Stage…
- Stent

- For patients with ileal loop
  - Place antegrade wires
Options for Biopsy

- Basket/Forceps
- Resection
- Laser
- Ablation of base
  - Laser
  - Cautery

Grade Correlates with Stage

- G1/2: 85% non-invasive*
- G3: 67% invasive*

- Accuracy of ureteroscopic biopsy for determining grade 80-92%**
  (compared to surgical pathology)

* AUA US 2005
** Guarzino et al, 2000
Appearance and Stage

• 85% of upper tract TCC are papillary*
  – 50% of papillary tumors invasive

• 15% sessile*
  – 80% of sessile tumors invasive

• Do you need tissue?
  *AUA US 2005

CORRELATION OF URETEROSCOPIC APPEARANCE WITH HISTOLOGIC GRADE OF UPPER TRACT TRANSITIONAL CELL CARCINOMA

ASSAAD EL-HAKIM, GARY H. WEISS, BENJAMIN R. LEE, AND ARTHUR D. SMITH

<table>
<thead>
<tr>
<th>Visual Impression of Grade on Ureteroscopy</th>
<th>Tumors (n)</th>
<th>Histologic Grade</th>
<th></th>
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</thead>
<tbody>
<tr>
<td>Low grade</td>
<td>28</td>
<td>Low Grade 1-2</td>
<td>High Grade 3-4</td>
</tr>
<tr>
<td></td>
<td></td>
<td>20 (71)</td>
<td>8 (29)</td>
</tr>
<tr>
<td>High grade</td>
<td>10</td>
<td>2 (20)</td>
<td>8 (80)</td>
</tr>
<tr>
<td>Benign</td>
<td>2</td>
<td>1 (50)</td>
<td>1 (50)</td>
</tr>
</tbody>
</table>

Data in parentheses are percentages.

• Only 70% accuracy
• Need tissue
Risk of Tumor Propagation

• Pyelovenous/tubular/lymphatic backflow
• Seeding of malignant cells

• Is ureteroscopy safe in setting of malignancy?

96 patients total NUx
• Half had ureteroscopy
• Similar demographic and tumor features
• 53 month follow-up
No Survival Difference

Who Should have Ureteroscopy?

- 66 male. HTN, ex-smoker. Normal GFR.
- Persistent micro-hematuria.
- Cytology (+)
- Flexible cystoscopy (-)
- CT IVP:
Who Should Have Ureteroscopy?

- Radiographic lesion - confirm diagnosis
- Nephron-sparing management
- Positive cytology no radiologic lesion

Percutaneous Approach

- Advantages
  - Larger instruments
  - Better for renal pelvic tumors
  - Tract may be used for topical therapy
- Disadvantages
  - Greater morbidity than ureteroscopy
  - Tract seeding
Antegrade Nephroscopy

- Forceps
- Resection
- Laser

- Ablation of base
  - Laser
  - Cautery

2nd Look Nephroscopy

- Advocated by some
- Performed 4-14 days later
- Look for residual or missed tumor
- Leave 8 fr nephrostomy tube if considering topical therapy

- 3rd look if residual tumor seen
Diagnosis

Management

Management Options

- Nephron-Sparing
  - Endoscopic; Laparoscopic; Open
- Radical
  - Laparoscopic; Open
- Adjuvant
  - Topical; systemic
Customizing Therapy

• Patient Factors
  – Age
  – Comorbidities/operative risk
  – Renal status
  – Urinary tract anatomy (previous diversion)

• Tumor Factors
  – Grade and stage
  – Size and location
  – Focality
  – Recurrent

Algorithm for Localized TCC

filling defect on radiograph/suspicion of upper tract TCC

R/O radiopaque calculus

ureteroscopy with biopsy of lesion

weigh risks of tumor progression/surgical risk/dialysis risks

nephroureterectomy
  high grade/volume
  normal kidneys
  poor compliance

conservative therapy
  low grade/volume
  abnormal kidney(s)
  poor surgical risk
Conservative Mgmt vs. Dialysis

![Graph showing survival rates for different stages of cancer and renal failure.]

**Stage**               | **5 yr CSS**
---                      | ---
**Ta, 1, CIS**           | 60-90%
**T 2**                  | 40-75%
**T 3**                  | 16-33%
**T 4**                  | 0-5%

- Better to be aggressive with invasive tumors and accept dialysis (if operative risk ok)
Open Nephroureterectomy

• GOLD STANDARD

• Indication
  – Large, high grade, invasive upper tract tumors
  – Large, recurrent, multifocal low grade tumors

• Decisions
  – 1 vs 2 incisions
  – lymphadenectomy
  – Bladder cuff technique

Positioning & Incision

• Flank +/- Torque
• Supine +/- Roll
Incision Options

- Single
  - Extended flank
  - Thoracoabdominal
  - Midline
- Double
  - Gibson
  - Pfannensteil
  - Low midline

Distal Ureter and Cuff of Bladder

- 30-75% stump recurrence

- Options
  - transvesical, extravesical, combination
  - Endoscopic: TUR, intussusception
Combined Transvesical/Extravesical

- Anterior cystotomy
- 1 cm circumscribe
- 2 layer closures
  - Hiatus
  - Cystotomy
- Foley + drain

Lymphadenectomy

- No therapeutic benefit shown
- Adds staging and prognostic information
- No evidence for adjuvant therapy

- Recommendation
  - Do it if it's easy
Results

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Campbell’s 9th Ed.

Laparoscopic Nephroureterectomy

- **Indications**
  - Same as open

- **Advantages**
  - Less morbid
  - Quicker convalescence
  - Equivalent cancer control (intermediate term)

- **Disadvantages**
  - Port site recurrence (case reports)
Positioning and Ports

Nephrectomy & Ureteric Dissection
Cuff - Options

- Open
- Endoscopic & Laparoscopic
  - Aggressive TUR
  - Intussusception
  - Transvesical (Gill)
  - Extravesical stapling

Transvesical (Gill, 1999)

- Bladder not closed
- Leave foley x 2 weeks
- Cystogram before foley removed
Extravesical Stapling

- Extraction incision anyway
- Why not open for distal ureter/cuff?

Review of 60 patients, LNUx
- 2/3 transves cuff; 1/3 extraves staple
- Similar groups
- 23 month f/u
- **Stapling worse**
  - Higher positive margin rate
  - Higher bladder recurrence rate
Follow-Up: Radical Surgery

• Cytology + Cystoscopy
  – q 3mo x 2 yr; q 6mo x 2yr; yearly thereafter

• CT Urogram
  – q 6mo x 2yr if high risk (>G2, > T1)
  – Yearly otherwise

• Metastatic work-up
  – CBC, Cr, LFTs, CXR
  – q 6mo x 2 yrs then yearly
  – q 3mo x 1 yr then as above if high risk

Results - Summary

<table>
<thead>
<tr>
<th>Investigator</th>
<th>LNU/OMU (n)</th>
<th>Bladder Recurrence (%)</th>
<th>Local Recurrence (%)</th>
<th>Distant Metastasis (%)</th>
<th>2yr Survival (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Shahin et al.⁶</td>
<td>13/13</td>
<td>23/53.8</td>
<td>15.3/0</td>
<td>15.3/23</td>
<td>77/69</td>
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<tr>
<td>McNeill et al.⁷</td>
<td>26/42</td>
<td>28/42</td>
<td>8/15.4</td>
<td>28/28</td>
<td>74/68</td>
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<tr>
<td>Kawachi et al.⁸</td>
<td>34/34</td>
<td>9/38</td>
<td>0/0</td>
<td>6.0/9.0</td>
<td>NA</td>
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<tr>
<td>Klingler et al.⁹</td>
<td>20/15</td>
<td>10.0/13.3</td>
<td>5.3/6.6</td>
<td>10.5/6.6</td>
<td>94.7/93.7</td>
</tr>
<tr>
<td>Rassweiler et al.¹⁴</td>
<td>23/21</td>
<td>34.8/14.4</td>
<td>0/4.8</td>
<td>17.4/28.5</td>
<td>89/63</td>
</tr>
<tr>
<td>Garibi et al.¹¹</td>
<td>28/42</td>
<td>28/42</td>
<td>4/15</td>
<td>28/18</td>
<td>NA</td>
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<tr>
<td>Tsuihara et al.¹³</td>
<td>25/24</td>
<td>28/33.3</td>
<td>n.a.</td>
<td>0/8</td>
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<tr>
<td>Present study</td>
<td>58/165</td>
<td>32.8/38.0</td>
<td>2.0⁺/1.0</td>
<td>17.2/19.9</td>
<td>85.2/87.0</td>
</tr>
</tbody>
</table>

NOTE: = transitional cell carcinoma; NA = not available; other abbreviations as in Table 1.
⁺ Post-site recurrence.
Comparative Study of Oncologic Outcome of Laparoscopic Nephroureterectomy and Standard Nephroureterectomy for Upper Urinary Tract Transitional Cell Carcinoma

Daisuke Manabe, Takashi Saika, Shin Ebara, Shinya Uehara, Atsushi Nagai, Ryuji Fujita, Shin Irie, Daisuke Yamada, Tomoyasu Tushima, Yasutomo Nasu, and Hiromi Kumon, for the Okayama Urological Research Group, Okayama, Japan

- Multi-institution review of 224 patients
- 58 LNUx ; 166 ONUx
- Open cuff excision in all LNUx
- Excluded patients with previous bladder Ca

Oncologic Results – 28 month f/u

<table>
<thead>
<tr>
<th></th>
<th>LNUx</th>
<th>ONUx</th>
</tr>
</thead>
<tbody>
<tr>
<td>Recurrence</td>
<td>33% bladder</td>
<td>38% bladder</td>
</tr>
<tr>
<td>Mets</td>
<td>17% distant</td>
<td>19% distant</td>
</tr>
<tr>
<td></td>
<td>1 port site met</td>
<td></td>
</tr>
<tr>
<td>Overall CS Survival</td>
<td>85%</td>
<td>87%</td>
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</tbody>
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Operation and Convalescence

<table>
<thead>
<tr>
<th>Shalhav et al. 2000</th>
<th>LNUx</th>
<th>ONUx</th>
</tr>
</thead>
<tbody>
<tr>
<td>OR time</td>
<td>7.7 hr</td>
<td>3.9 hr</td>
</tr>
<tr>
<td>EBL</td>
<td>199 cc</td>
<td>441 cc</td>
</tr>
<tr>
<td>LOS</td>
<td>3.6 days</td>
<td>9.6 days</td>
</tr>
<tr>
<td>Complications</td>
<td>Major 8%</td>
<td>Major 29%</td>
</tr>
<tr>
<td></td>
<td>Minor 10%</td>
<td>Minor 29%</td>
</tr>
</tbody>
</table>

LNUX – Bottom Line

- Less morbidity
- Similar oncologic results with short term data
NSS - Indications

• < G2, ≤ T1, < 2cm solitary tumors
• Absolute
  – Bilateral tumors
  – Solitary kidney
  – Renal insufficiency
  – Poor operative risk
• Relative
  – Balkan nephropathy
  – Potential for contralateral renal compromise

NSS - Options

<table>
<thead>
<tr>
<th>Endoscopic</th>
<th>Open</th>
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<tbody>
<tr>
<td>Perc Neph URS</td>
<td>Pyelotomy + Resection</td>
</tr>
<tr>
<td>URS</td>
<td>Segmental Ux UU/Boari + PH</td>
</tr>
<tr>
<td>URS</td>
<td>Segmental Ux UU/Boari + PH</td>
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<tr>
<td>URS</td>
<td>Distal Ux Reimplant</td>
</tr>
</tbody>
</table>
Endoscopic vs Open NSS

• Ideal Tumor:
  - < 2cm
  - < G2
  - solitary
  - easy to get to
• Ideal Patient:
  - poor operative risk

• Ideal Tumor:
  - > 2cm
  - > G2, >T2
  - multifocal
  - distal ureter
• Ideal patient:
  - need nephron sparing
  - good operative risk

Follow-Up: NSS

• Cysto & cytology
  - q 3mo x 1 yr then q 6mo
• US/IVP/CT IVP
  - q 3mo x 1 yr then q 6mo
  - RPG if equivocal
• Repeat URS if cytology (+) or radiologic finding

Goel et al. 2003
### NSS – PCN Results

<table>
<thead>
<tr>
<th></th>
<th>N</th>
<th>F/U (yr)</th>
<th>G3</th>
<th>Recur</th>
<th>NUx</th>
<th>CSS</th>
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<tr>
<td>Jarrett 1995</td>
<td>35</td>
<td>4.5</td>
<td>36%</td>
<td>33%</td>
<td>25%</td>
<td>83%</td>
</tr>
<tr>
<td>Palou 2004</td>
<td>34</td>
<td>4.4</td>
<td>41%</td>
<td>27%</td>
<td>26%</td>
<td>94%</td>
</tr>
<tr>
<td><strong>Significant proportion got NUx</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Stream 1999</td>
<td>18</td>
<td>2</td>
<td>22%</td>
<td>33%</td>
<td>14%</td>
<td>82%</td>
</tr>
<tr>
<td>Smith 2001</td>
<td>69</td>
<td>4</td>
<td>28%</td>
<td>36%</td>
<td>14%</td>
<td>84%</td>
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<tr>
<td>Goel 2003</td>
<td>20</td>
<td>5.3</td>
<td>40%</td>
<td>40%</td>
<td>40%</td>
<td></td>
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### Summary of URS

<table>
<thead>
<tr>
<th>Authors</th>
<th>Year</th>
<th>Patients</th>
<th>Procedure</th>
<th>Recurrence</th>
<th>HT (%)</th>
<th>Non-Responders</th>
<th>Follow-up</th>
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<td>Iffert et al.</td>
<td>1985</td>
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<td>Balian et al.</td>
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<td>Johnson, 1992</td>
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<td>Cremosa et al.</td>
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<td>Tava et al.</td>
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<td>Kistner et al.</td>
<td>1994</td>
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<td>Bana et al.</td>
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<td>Morin et al.</td>
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<td>Prévot and Pothier</td>
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<td>Serisier et al.</td>
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<td>Elliott et al.</td>
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</table>
Topical Therapy

• No established role
• Difficulty administering

• Studies small, short-term, not controlled

• Persistent positive UT cytology = CIS
  – Controversial…

NSS – Bottom Line

• Recurrence common – 40%
  – Need more stringent surveillance
  – Need for repeat treatments
• Eventual nephroureterectomy – 25%
  – In operative candidates
• Grade (stage) determines outcome

Feasible option for low-grade focal tumors
  – Especially if poor operative candidate
Metastatic Disease

• Treated with chemo regimens as for bladder TCC
  – MVAC, GC

• No trials given rarity of disease

Summary

• Upper Tract TCC is rare
• Invasion and mets common
• Ureteroscopy adds diagnostic accuracy
• Management tailored to patient and pathology characteristics
• Laparoscopic NUx = Open Nux in short term
• Endoscopic approach feasible for low grade and lower operative risk
  – Recurrence common, need multiple treatments
THANK YOU