When to Integrate Surgery for Metastatic Urothelial Cancers

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Case Presentation #1

- 67 yo male with gross hematuria
- No constitutional symptoms
- Mild LLE peripheral neuropathy - ? Etiology
- PMH and PSHx negative
- Exam negative other than LLE paresthesia
- Labs:
  - UA: TNTC RBC
  - Hgb 14.8
  - Serum Cr 1.1 (eGFR 65)
- Cystoscopy normal
- Cytology suspicious
CT Scan
Case Presentation #1

- CT chest negative for mets
- Ureteroscopy inconclusive
- Renal biopsy consistent with Urothelial CA
- Given locally advanced features – patient recommended for neoadjuvant chemotherapy
Post-Chemotherapy CT
Post-Chemotherapy CT
Pathology

- pT3 N0 urothelial carcinoma
- Negative margins
- 24 nodes negative for metastases

- However……
3 Months Post-Op CT/PET
Management Questions

• How do metastases affect management recommendations for Urothelial Cancers?
  – Nodal mets (pelvic vs. retroperitoneal vs. both)
  – Distant nodal or visceral mets (solitary vs. multiple)

• Is there a role for cystectomy in patients with retroperitoneal nodal mets or distant mets?

• What is the role of metastasectomy? When?
Metastatic Urothelial Cancer

- Cisplatin-based chemo
  - Response rate 44% to 64%
  - But…overall survival poor 14-15 months
- Is there a surgical role for selected patients with urothelial cancer and de novo metastases or metastatic progression?

Integrating Surgery for Metastatic Urothelial Cancer

• Early evidence for metastasectomy
• Cowles, Johnson et al (MDACC)…
  – 6 patients with delayed oligo pulmonary metastases from urothelial cancer
  – s/p thoracic wedge resection
  – Median OS 5 years

• Small phase II study
  – 11 patients
  – Biopsy proven TCC in retroperitoneal nodes
  – No evidence of visceral mets
  – “Significant” response to chemotherapy
  – Underwent bilateral RPLND

• Study end point - disease specific survival

Post-Chemo RPLND for Metastatic Urothelial Cancer

- RPLND delayed in 4 & concurrent with RC & PLND in 7
- 9 pts with residual viable tumor in retroperitoneal nodes
- Recurrence and progression
  - 7 with recurrence outside surgical field
    - Median time to recurrence = 7 months
  - Overall median DSS = 14 months
  - Overall median RFS = 7 months.
  - Four-year DSS = 36%
  - Four-year RFS = 27%
- Viable tumor in ≤ 2 nodes – increased DSS and RFS (p=0.006 and p=0.01, respectively).
• Retrospective multi-institutional study of 44 patients s/p complete resection of all detectable metastases (17 year period)

• Endpoints: overall, cancer-specific and progression-free survival

# Surgery for Metastatic Urothelial Cancer


<table>
<thead>
<tr>
<th>Patient characteristics</th>
<th>No. of Patients</th>
<th>%</th>
</tr>
</thead>
<tbody>
<tr>
<td>Total</td>
<td>44</td>
<td>100</td>
</tr>
<tr>
<td>Men</td>
<td>29</td>
<td>65.9</td>
</tr>
<tr>
<td>Women</td>
<td>15</td>
<td>34.1</td>
</tr>
<tr>
<td>Primary tumor site</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Bladder</td>
<td>35</td>
<td>79.5</td>
</tr>
<tr>
<td>Upper urinary tract</td>
<td>9</td>
<td>20.5</td>
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<tr>
<td>Sequence of treatment for metastases</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Surgery only</td>
<td>9</td>
<td>20.5</td>
</tr>
<tr>
<td>Surgery + chemotherapy</td>
<td>13</td>
<td>29.5</td>
</tr>
<tr>
<td>Chemotherapy + surgery</td>
<td>16</td>
<td>36.4</td>
</tr>
<tr>
<td>Chemotherapy + surgery + chemotherapy</td>
<td>6</td>
<td>13.6</td>
</tr>
<tr>
<td>Metastatic sites resected</td>
<td></td>
<td></td>
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<tr>
<td>RP lymph nodes (above aortic bifurcation)</td>
<td>25</td>
<td>56.8</td>
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<tr>
<td>Distant lymph nodes</td>
<td>5</td>
<td>11.3</td>
</tr>
<tr>
<td>Lung</td>
<td>8</td>
<td>18.2</td>
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<tr>
<td>Bone</td>
<td>2</td>
<td>4.5</td>
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<tr>
<td>Adrenal gland</td>
<td>1</td>
<td>2.3</td>
</tr>
<tr>
<td>Brain</td>
<td>1</td>
<td>2.3</td>
</tr>
<tr>
<td>Small intestine</td>
<td>1</td>
<td>2.3</td>
</tr>
<tr>
<td>Subcutaneous</td>
<td>1</td>
<td>2.3</td>
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</table>
Survival Results

- No significant prognostic factors were identified
  - Age, gender, metastatic site, or duration/type of chemotherapy
- Seven patients survived for >2 yr
  - remained free from progression at median of 63 mo
  - Nodes (3), Lungs (3), bone (1)

– 42 patients - resection of urothelial carcinoma metastases with curative intent
– Nearly all (41) received chemotherapy before and/or after metastasectomy
– Metastasectomy:
  • 20 lymph node dissections
  • 12 pulmonary resections
  • 5 pelvic exenteration or resection for local recurrence
  • 2 resections for subcutaneous metastasis
  • 1 liver resection
  • 2 “other” resections
– Repeat metastasectomy (7 patients)
Metastasectomy for Urothelial Cancer

- **Primary tumor site:**
  - 21 Bladder
  - 18 Upper urinary tract
  - 3 Combined

- **Metastatic sites:**
  - 39 patients involving a single organ site
  - 3 patients involving multiple organ sites

- **Number of mets:**
  - Oligometastatic in 23 patients
  - 2 or more metastases in 14 patients
  - ≥ 3 in 5

- **Timing of metastases:**
  - Metachronous in 36 patients after resection of the primary
  - Synchronous in 6 – present at original diagnosis of primary cancer

Metastasectomy for Urothelial Cancer

• Pathology:
  – Viable cancer in 30 patients
  – Necrosis in 12 of 34 patients who received systemic chemo before metastasectomy

## Univariate analysis of prognostic significance after metastasectomy

<table>
<thead>
<tr>
<th></th>
<th>No. Pts</th>
<th>Median Mos Survival</th>
<th>p Value</th>
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<tbody>
<tr>
<td><strong>Male</strong></td>
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<td>26</td>
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</tr>
<tr>
<td><strong>Female</strong></td>
<td>13</td>
<td>31</td>
<td>0.2064</td>
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<tr>
<td><strong>Age:</strong></td>
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<td></td>
</tr>
<tr>
<td>Less than 68</td>
<td>21</td>
<td>21</td>
<td></td>
</tr>
<tr>
<td>68 or Greater</td>
<td>21</td>
<td>29</td>
<td>0.9988</td>
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<td><strong>Primary site:</strong></td>
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<tr>
<td>Bladder</td>
<td>21</td>
<td>21</td>
<td></td>
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<tr>
<td>Other</td>
<td>21</td>
<td>34</td>
<td>0.9713</td>
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<tr>
<td><strong>Primary surgery-metastasis disease-free interval (mos):</strong></td>
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<td></td>
<td></td>
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<tr>
<td>Less than 12</td>
<td>17</td>
<td>23</td>
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<tr>
<td>12 or Greater</td>
<td>25</td>
<td>26</td>
<td>0.9077</td>
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<tr>
<td>Less than 24</td>
<td>30</td>
<td>26</td>
<td></td>
</tr>
<tr>
<td>24 or Greater</td>
<td>12</td>
<td>26</td>
<td></td>
</tr>
<tr>
<td><strong>Chemotherapy before metastasectomy:</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Yes</td>
<td>34</td>
<td>26</td>
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<tr>
<td>No</td>
<td>8</td>
<td>29</td>
<td>0.9498</td>
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<td><strong>Metastatic site:</strong></td>
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<tr>
<td>LN only</td>
<td>19</td>
<td>26</td>
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<tr>
<td>Lung only</td>
<td>12</td>
<td>34</td>
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<tr>
<td>Other</td>
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<tr>
<td>LN or lung</td>
<td>32</td>
<td>31</td>
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<tr>
<td>Other</td>
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<td>11</td>
<td>0.1933</td>
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<tr>
<td><strong>Solitary LN or solitary lung</strong></td>
<td>15</td>
<td>81</td>
<td>0.0296</td>
</tr>
<tr>
<td><strong>Other</strong></td>
<td>27</td>
<td>19</td>
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</tr>
</tbody>
</table>
Kaplan-Meier Analysis of Overall Survival, Abe et al.

A, From initiation of treatment. B, From time of metastasectomy. C, From time of metastasectomy in patients with solitary lung or solitary LN metastasis (blue curve) vs. others (red curve).
Retrospective study of 30 patients (14 years)
- 10/30 with mixed or nonurothelial primaries (adenocarcinoma, squamous)
- Excluded cT4b &/or cN1-N3 patients that received chemo followed by RC and PLND
- Some underwent ≥ 2 metastasectomies
- Only 1 patient with M+ tumor at diagnosis
## Sites and Characteristics of Resected Metastases (n = 30)

<table>
<thead>
<tr>
<th>Resected Site</th>
<th>Additional Metastasectomy</th>
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</thead>
<tbody>
<tr>
<td>Lung</td>
<td>24 (80) No</td>
</tr>
<tr>
<td>Liver</td>
<td>2 (7) Yes</td>
</tr>
<tr>
<td>Bone</td>
<td>1 (3) 1 More</td>
</tr>
<tr>
<td>Lymph node</td>
<td>3 (10) 2 More</td>
</tr>
<tr>
<td></td>
<td>4 More</td>
</tr>
</tbody>
</table>

Metastasectomy in Urothelial Cancer

• Max diameter of pulmonary mets
  – < 3 cm in 18 patients (75%)
  – ≥ 3 cm in 6 patients (25%)
• 28/30 - metastasectomy as initial treatment
• 11/30 received postop chemo
  – Gem / Cis (6)
  – Gem / Carbo (3)
  – MVAC (2)
• 2/30 received preop chemo

(A) OS & TTP following metastasectomy
- Median OS = 30.0 months from metastasectomy
- 3-year OS rate = 41%
- 18 patients with disease progression/relapse & median TTP = 15.2 mo

(B) Nonpulmonary metastasectomy – the only independent prognostic factor affecting OS (Hazard Ratio, 9.10; \( P = .001 \))

Metastasectomy in Urothelial Cancer

• Pulmonary metastasectomy vs. nonpulmonary metastasectomy (bone or liver)
  – TTP (26 months vs. 3 months)
  – OS (43 months vs. 13 months)

• Advocate for chemo prior to metastasectomy
  – Yet…no significant correlation in this study between perioperative chemo and improved OS in this study

• Trend towards improved response in non-pure urothelial tumors

Case Presentation #2

• 67 yo male with gross hematuria
• ECOG = 0
• Past Hx non-contributory
• Very active
• Normal sexual function
• Normal physical exam
• Cysto – Large volume tumor occupying bladder floor and right trigone
Case Presentation #2

- **Staging:**
  - TURBT – muscle invasive urothelial cancer with T3b tumor on EUA
  - CT Chest negative
  - CT A/P
    - Large volume bladder tumor
    - Pelvic lymph node mets
    - Multiple retroperitoneal lymph node mets
    - Right hydrenephrosis
- cT3b, N3, M1 Urothelial cancer
Pre-treatment Axial CT
Pre-treatment Coronal CT
Case Presentation #2

• Patient managed with Gem/Cis x 6 cycles
• Repeat endoscopic and radiographic staging:
  – Moderate volume bladder tumor remains with extension to right bladder pedicles
  – CR with pelvic and retroperitoneal nodes
Post-treatment Axial CT
Post-treatment Coronal CT
Case #2 Outcome

• Initial Stage cT3bN3M1 Urothelial Carcinoma

• Management:
  1. Radical cystoprostatectomy with ileal conduit
  2. Post-chemo RPLND and PLND

• Pathology = T3bN3M1 tumor
  • Micropapillary features
  • pT3b Margins negative (clinically suspect R1)
  • Pelvic nodes (1/18 nodes +)
  • Retroperitoneal nodes (2/16 nodes +)
Case #2 Outcome

- Adjuvant XRT to pelvis (right pararectal)
  - Declined adjuvant chemo
- NED x 8 months
Guidelines for Patient Selection & Surgical Resection

• Patients should receive systemic therapy first
  – Some patients might do well with surgery alone

• CR or PR to systemic therapy
  – ?? “defined” period of disease stability

• Best surgical candidates…
  – Limited nodal or solitary lung met (occasional solitary visceral met)

• Poor surgical candidates…
  – Complete surgical resection not feasible
  – Multiple liver metastases
  – Metastases involving more than one visceral site
  – Bone metastases - especially involving pelvis or axial skeleton (disease often more extensive than appreciated)