Case Based Decision-Making for Treatment of MIBC

Seth P. Lerner, MD, FACS
Professor of Urology
Beth and Dave Swalm Chair in Urologic Oncology
Scott Department of Urology
Baylor College of Medicine, Houston, Texas
Disclosures

• Clinical trials
  – Endo, FKD, JBL (SWOG), Roche/Genentech (SWOG), Viventia

• Consultant
  – BioCancell, UroGen, Vaxiion

• Advisory Board
  – BioCancell, miR Scientific, QED Therapeutics, UroGen
How common are variant histologies?

- Variant histologies found in 6-25% of TUR samples: depends how hard you look and how experienced the pathologist
- **AUA Guidelines**: an experienced genitourinary pathologist should review the pathology of a patient when variant histology is suspected or if muscle invasion is equivocal
- **EAU Guidelines**

<table>
<thead>
<tr>
<th>Pathological report</th>
<th>Rating</th>
</tr>
</thead>
<tbody>
<tr>
<td>The pathological report should specify tumour location, tumour grade, depth of tumour invasion, presence of CIS, and whether the detrusor muscle is present in the specimen.</td>
<td>A</td>
</tr>
<tr>
<td>The pathological report should specify the presence of lymphovascular invasion or unusual (variant) histology.</td>
<td>C</td>
</tr>
<tr>
<td>In difficult cases, consider an additional review by an experienced genitourinary pathologist.</td>
<td>B</td>
</tr>
</tbody>
</table>

WHO Classification of Urothelial Tumors

Urothelial Carcinoma: Histologic Variants:

- Urothelial carcinoma, NOS
- Invasive UC with squamous differentiation (vs. Squamous cell Ca)
- Invasive UC with glandular differentiation (vs. Adenocarcinoma)
- Urothelial carcinoma with trophoblastic differentiation
- Nested variant
- Microcystic variant
- Micropapillary variant
- Small cell carcinoma
- Lymphoepithelioma-like carcinoma
- Plasmacytoid variant
- Sarcomatoid variant (with and without heterologous elements)
- Urothelial carcinoma with giant cells
- Clear cell variant
- Lipoid cell variant
- Undifferentiated carcinoma

……

Courtesy Hikmat Al-Ahmadie
**Historic non-urothelial histology incidence**

**National Cancer Data Base:**

163,683 BCa (1998-2014) $\Rightarrow$ 10,421 (6.4%) non-urothelial histo

- 2.4% $\Rightarrow$ squamous cell cancer (SCC)
- 1.7% $\Rightarrow$ adenocarcinoma (AC)
- 1.3% $\Rightarrow$ neuroendocrine (NE)

Royce et al., Urol Oncol 2017
Historic non-urothelial histology

10,421 (6.4%) non-urothelial histology vs UCB
⇒ more likely to be…

- younger: 65 vs 66 yrs (?)
- female: 36-62% vs 26%
- muscle invasive: 43% vs 33%
- metastatic: 18-31% vs 12%

Royce et al., Urol Oncol 2017
Urothelial variant histology confers worse prognosis

<table>
<thead>
<tr>
<th>Outcome (CSS or OS)</th>
<th>Predictor</th>
<th>HR (95% CI)</th>
<th>P value</th>
<th>Coefficient (95% CI)*</th>
<th>Prognostic score¹</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>CSS</strong></td>
<td>Age (yrs): &lt;65 vs. ≥65</td>
<td>2.107 (1.170 to 3.797)</td>
<td>0.013</td>
<td>0.745 (0.189 to 1.580)</td>
<td>2</td>
</tr>
<tr>
<td></td>
<td>pT stage: ≤pT1 vs. ≥pT3</td>
<td>3.791 (1.525 to 9.421)</td>
<td>0.004</td>
<td>1.333 (0.519 to 2.425)</td>
<td>4</td>
</tr>
<tr>
<td></td>
<td>pN stage: pN0 vs. ≥pN1</td>
<td>2.937 (1.575 to 5.476)</td>
<td>0.001</td>
<td>1.077 (0.377 to 1.818)</td>
<td>4</td>
</tr>
<tr>
<td></td>
<td>Margin status: negative vs. positive</td>
<td>2.509 (1.101 to 5.716)</td>
<td>0.029</td>
<td>0.920 (−0.670 to 1.755)</td>
<td>2</td>
</tr>
<tr>
<td></td>
<td>Histology: pure vs. variants except squamous differentiation</td>
<td>4.577 (1.835 to 11.413)</td>
<td>0.001</td>
<td>1.521 (0.118 to 2.832)</td>
<td>4</td>
</tr>
<tr>
<td><strong>OS</strong></td>
<td>Age (yrs): &lt;65 vs. ≥65</td>
<td>2.856 (1.819 to 4.485)</td>
<td>&lt;0.001</td>
<td>1.050 (0.611 to 1.620)</td>
<td>4</td>
</tr>
<tr>
<td></td>
<td>pT stage: ≤pT1 vs. ≥pT3</td>
<td>3.310 (1.738 to 6.301)</td>
<td>&lt;0.001</td>
<td>1.197 (0.615 to 1.930)</td>
<td>4</td>
</tr>
<tr>
<td></td>
<td>pN stage: pN0 vs. ≥pN1</td>
<td>2.660 (1.645 to 4.303)</td>
<td>&lt;0.001</td>
<td>0.978 (0.419 to 1.524)</td>
<td>3</td>
</tr>
<tr>
<td></td>
<td>Histology: pure vs. variants except squamous differentiation</td>
<td>2.717 (1.209 to 6.109)</td>
<td>1.000</td>
<td>1.000 (0.048 to 2.046)</td>
<td>3</td>
</tr>
</tbody>
</table>

Ku, et al Bladder Cancer 4:195, 2018
64yo Male with Gross Hematuria

- Smoker: 1.5 pack/day for 30 years
- Co-morbidities: HTN, HL
- eGFR 90
- US: Single bladder mass
- Cytology: positive
- Cystoscopy:
  - Single lesion on the left side
  - Appearance: papillary tumor of 2cm
pT1 high grade urothelial carcinoma:

✓ Primary, size 2 cm
✓ Concomitant focal CIS,
✓ Visually complete resection,
✓ Detrusor in the specimen,
✓ No lymphovascular invasion,
✓ Variant histology: 30% micropapillary
Primary pT1 HG unifocal 2cm UCB with concomitant CIS & micropapillary variant, completely resected

What would you do next?
1) Path re-review to verify (percentage of micropapillary)
2) Intravesical BCG ± maintenance
3) Re-TURBT
4) Radical cysto-prostatectomy
Micropapillary Variant

- Pattern may be focal, extensive or exclusive
- **Papillary-type** structures within single retracted space
- HER2 amplification
- Aggressive behavior with **high metastatic rate**
  - >95% are muscle-invasive at time of presentation
  - CIS & lymphovascular invasion > 50% of cases

Moschini et al., Nature Rev Urol 2017
Re-TURBT

Ta HG UCB with: 30% micropapillary pattern
Concomitant focal CIS
No LVI

Which therapy do you recommend?

1. Re-re-TURB ± BCG
2. Intravesical BCG ± maintenance
3. Intravesical chemotherapy ± maintenance
4. Radical cysto-prostatectomy
## Micropapillary variant

<table>
<thead>
<tr>
<th>Author, Year</th>
<th>cT1N0</th>
<th>Early RC, n (%)</th>
<th>FU (mo)</th>
<th>upstage (5y CSS)</th>
<th>TURB, n (%)</th>
<th>FU (mo)</th>
<th>BCG</th>
<th>Prog (5y CSS)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Comperat et al., 2010</td>
<td>33</td>
<td>26</td>
<td>16&lt;sup&gt;2&lt;/sup&gt;</td>
<td>19 (73)</td>
<td>NR</td>
<td>7</td>
<td>NR</td>
<td>NR</td>
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<tr>
<td></td>
<td>47</td>
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<tr>
<td>Holyoak et al., 2013</td>
<td>(≤T1)</td>
<td>3</td>
<td>NR</td>
<td>NR</td>
<td>(100)</td>
<td>44</td>
<td>NR</td>
<td>NR</td>
</tr>
<tr>
<td>Spaliviero et al., 2014</td>
<td>36</td>
<td>15</td>
<td>30</td>
<td>5 (33)</td>
<td>(81)</td>
<td>21</td>
<td>36</td>
<td>16 (76)</td>
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<tr>
<td>Jackson et al., 2014</td>
<td>24</td>
<td>7</td>
<td>31</td>
<td>2 (29)</td>
<td>NR</td>
<td>17</td>
<td>32</td>
<td>10 (59)</td>
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<td></td>
<td></td>
<td>40</td>
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<tr>
<td>Willis et al., 2015</td>
<td>72</td>
<td>26</td>
<td>72</td>
<td>6 (23)</td>
<td>(100)</td>
<td>40</td>
<td>56</td>
<td>18 (45)</td>
</tr>
<tr>
<td>Fernandez et al., 2017</td>
<td>38</td>
<td>38</td>
<td>72</td>
<td>NR</td>
<td>(90)</td>
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<td></td>
<td>34</td>
<td></td>
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</tr>
<tr>
<td>Sui et al., 2016</td>
<td>166</td>
<td>33</td>
<td>NR</td>
<td>20 (62)</td>
<td>NR</td>
<td>133</td>
<td>NR</td>
<td>NR</td>
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<tr>
<td>Tripathi et al., 2017</td>
<td>96</td>
<td>---</td>
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<td>---</td>
<td>---</td>
<td>96</td>
<td>NR</td>
<td>NR</td>
</tr>
</tbody>
</table>

- **Upstaging/Progression:** 23 - 73% vs. 18 - 45%
- **5y CSS:** 81 - 100% vs. 60 - 85%

> Some patients seem to benefit from bladder sparing strategies.
BCG induction than @ 3 months: cytology positive with normal cystoscopy

What would you do next?

1. Radical cystoprostaticctomy
2. TURBT with Hexvix (or mapping biopies) with selective cytologies upper tracts & prostate TUR
3. Continue BCG maintenance
4. BCG re-induction
Case 1: Next Steps

- Received re-induction BCG
- @ 6 months: papillary lesion T2 HG (30% micropapillary) with concomitant focal CIS
- Staging CT normal

What would you next?

1. Radical cystoprostatetcomy
2. Neo-adjuvant systemic chemotherapy
3. Trimodal therapy (TUR/chemoRx/radiotherapy)
4. Partial cystectomy
Micropapillary variant

Preoperative chemotherapy vs. RC alone

<table>
<thead>
<tr>
<th>Study or Subgroup</th>
<th>1.1.2 Cancer-specific survival</th>
<th>Hazard Ratio IV, Fixed, 95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>Canvasser 2014</td>
<td>38.5% 0.90 (0.32, 2.95)</td>
<td></td>
</tr>
<tr>
<td>Fernandez 2017</td>
<td>67.7% 0.96 (0.49, 1.98)</td>
<td></td>
</tr>
<tr>
<td>Heterogeneity: CI² = 0.00, df = 1 (P = 1.00), I² = 0%</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Test for overall effect: Z = 0.32 (P = 0.75)</td>
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</tbody>
</table>

Radical cystectomy: MP vs. UC

- Neo-adjuvant chemotherapy associated with downstaging but not impact on survival
- MP variant not associated with worse survival outcomes after RC

Forster et al., in submission
Case 2

- 65 yo male
- History of colon cancer 23 yrs prior
  - Low anterior resection
  - Chemo/radiation therapy
- Recent dx Parkinson’s Disease
- Gross hematuria
Case 2

- Tumor high on the dome
- TURBT path: HG urothelial with extensive squamous differentiation (90%) – cT2NxMx
- eGFR 63
Next Steps?

1) Verify maximal TURBT and bladder preservation with chemo/radiation therapy
2) Pre-op neoadjuvant radiation followed by radical cystectomy
3) Radical cystectomy
4) Neo-adjuvant chemotherapy followed by radical cystectomy
5) Bladder preservation
Trimodal Bladder Sparing Therapy & Variant Histology

- MGH 1993-2013; T2-T4aN0M0
- 303 patients; 63 (22%) variant histology
- 76% squamous or glandular differentiation
- 12% sarcomatoid; 4.5% micropapillary or neuroendocrine
- 83% initial CR – no difference between variant and pure urothelial
- Variant histology not an independent prognostic variable

Krasnow et al Eur Urol 72:54, 2017
Trimodal Bladder Sparing Therapy and Variant Histology

10 year RC rate
Pure UC 19%
Variant UC 28%

Next steps – RC +/- Neoadjuvant chemotherapy

Guidelines – AUA, EAU, ASCO

• Neo-adjuvant chemotherapy with cis-platin based multi-agent regimen standard of care
  - AUA: Strong Recommendation; Evidence Level: Grade B
• M-VAC/CMV only regimens tested in Phase III trials
• Common use of GC based on patients with metastatic disease and has not been evaluated in Phase III neoadjuvant trials
SWOG 8710 Neoadjuvant M-VAC- Benefit cT2 vs. cT3-T4a

*Pts with cT2 also benefit from neoadjuvant chemotherapy*

### TABLE 4 Estimated hazard ratios

<table>
<thead>
<tr>
<th>Model</th>
<th>Patients included in the model</th>
<th>N</th>
<th>Contrast</th>
<th>HR</th>
<th>95% CI</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Mixed tumours</td>
<td>59</td>
<td>MVAC vs cystectomy-only</td>
<td>0.46</td>
<td>(0.25–0.87)</td>
<td>0.02</td>
</tr>
<tr>
<td>2</td>
<td>Pure UC</td>
<td>236</td>
<td>MVAC vs cystectomy-only</td>
<td>0.90</td>
<td>(0.67–1.21)</td>
<td>0.48</td>
</tr>
<tr>
<td>3</td>
<td>MVAC + cystectomy</td>
<td>147</td>
<td>Mixed vs pure UC</td>
<td>0.69</td>
<td>(0.42–1.13)</td>
<td>0.14</td>
</tr>
<tr>
<td>4</td>
<td>Cystectomy-only</td>
<td>148</td>
<td>Mixed vs pure UC</td>
<td>1.28</td>
<td>(0.80–2.06)</td>
<td>0.30</td>
</tr>
</tbody>
</table>

HR, hazard ratio, adjusted for age and clinical stage; 95% CI, 95% confidence intervals; UC, urothelial carcinoma; MVAC, methotrexate, vinblastine, doxorubicin and cisplatin.
• **AUA**: There are no validated predictive factors or clinical characteristics associated with an increased or decreased probability of response and benefit using cisplatin-based NAC.

• **EAU**: No tools are available to select patients who have a higher probability of benefitting from NAC. In the future, genetic markers, in a personalised medicine setting, might facilitate the selection of patients for NAC.
Next steps?

- Re-staging after 4 cycles NAC with Gem/Cis
  - Necrotic tissue overlying viable tumor on dome

What would you do:

1. RC with standard PLND (common iliac bifurcation)
2. RC with extended PLND (aortic bifurcation)
3. Radiation alone
4. Radiosensitizer + radiation
Next Steps?

- Radical cystectomy
  - RC and modified ePLND – could not do left CI
  - Difficult dissection of rectum off of bladder and prostate
  - Non-nerve sparing
- Path: pT2aN0 (0/25) with multifocal CIS and 99% squamous differentiation
- Role for adjuvant therapy?
Neuroendocrine Cancer

- Small cell
- Large cell
- Well-differentiated
- Paraganglioma
  \[ \Rightarrow \text{borderline features (very good prognosis)} \]
  \[ 93.5\% \, @ \, 5\text{-year OS} \]
Case 3

- 65 y/o healthy male
- cT3 N0 UC with small cell features
- eGFR 55 ml/min
Case 3 – Next steps?

1) Radical cysto-prostatectomy
2) Neo-adjuvant chemotherapy with MVAC or GC
3) Neo-adjuvant chemotherapy with Gem+ carboplatin
4) Neo-adjuvant chemotherapy with Etoposide + cisplatin
Small Cell Variant

- May be predominant or mixed
- Aggressive, prognosis poor, paraneoplastic syndromes
  - ACTH, hypercalcemia, hypophosphatemia
- Treatment requires neoadjuvant chemotherapy (cisplatin and etoposide) followed by radical cystectomy or radiation therapy.
Small cell cancer

⇒ 125pts (cT<4) ⇒ 48 chtx+CR ⇒ pT0 in 62%
Case 3

Completed 4 cycles of EP chemo with clinical complete response. Next steps?

1) Observation
2) Intravesical therapy
3) RC with bilateral lymphadenectomy
4) Radiation therapy to bladder & pelvic lymph nodes
### Association Between Disease Stage and Brain Metastases

| Brain Metastasis | Disease Stage (No. of patients) |  
|------------------|--------------------------------|---|
|                  | II                             | III | IV  |
| No               | 14                             | 2   | 6   |
| Yes              | 0                              | 2   | 6   |

NOTE: Generalized Fisher exact test: $P = .004$

50% Incidence $\geq$T3b, N+, or M+  

Case 3 – Outcome

- Etoposide/cisplatin x4 cycles
- Radical cystectomy, extended PLND and RPLND
- pT1N0 in bladder residual UC only (no small cell)
- Alive and NED after 5 years
MANAGEMENT OF MIBC WITH VARIANT HISTOLOGY

Bladder tumor

TURBT and clinical staging (including examination under anesthesia)

Muscle invasive disease

Conventional UC, squamous or glandular differentiation, nested variant, other rare variants

T2aN0M0

T3-T4aN0M0

LVI hydunehrosis

Neoadjuvant chemotherapy

Sarcomatoid, plasmacytoid, micropapillary (T2-T4)

Small cell (T2-T4)

+ Squamous cell or adenocarcinoma

Consider preoperative XRT for pT3-T4 squamous cell carcinoma

Cystectomy

Willis et al., Curr Opin Urol 2013