Management of Non-Muscle Invasive Bladder Cancer

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Non-muscle Invasive Bladder Cancer

- **Tx** – cannot be assessed
- **T0** – No evidence of primary tumor
- **Ta** – Noninvasive papillary carcinoma
- **Tis** – Carcinoma in situ
- **T1** – Invades lamina propria
- **T2** – Invades muscularis propria
  - **T2a** – inner half
  - **T2b** – outer half
- **T3** – Invades perivesical tissue
  - **T3a** – microscopically
  - **T3b** – macroscopically
- **T4** – Invades adjacent structures:
  - **T4a** – prostatic stroma, uterus, vagina
  - **T4b** – pelvic wall, abdominal wall
Bladder Cancer

- Muscle Invasive (~30%)
- Non-muscle Invasive (~70%)
  - Low risk (~50%)
  - Int/High risk (~50%)
Non-Muscle Invasive Bladder Cancer

- Recurrence rate of 50-90%
- Progression to muscle invasive disease 10-20%

Siegel et al. Cancer Statistics 2015
David et al. Cancer, 2009
Non-Muscle Invasive Bladder Cancer

- SEER-Medicare Evaluation of > 7000 patients with high-grade NMIBC
  - 39% recurrence without progression
  - 33% progression rate
    - Female
    - AA race
    - Undifferentiated grade
    - CIS/T1
  - 13% died due to bladder cancer

NMIBC Focus Points

- Risk Adjusted Treatment
- Repeat TURBT – within 6 weeks
- Intravesical Therapy – BCG Maintenance
- Technology utilization
- Use of Radical Cystectomy
<table>
<thead>
<tr>
<th>Low Risk</th>
<th>Intermediate Risk</th>
<th>High Risk</th>
</tr>
</thead>
<tbody>
<tr>
<td>LG&lt;sup&gt;a&lt;/sup&gt; solitary Ta ≤ 3cm</td>
<td>Recurrence within 1 year, LG Ta</td>
<td>HG T1</td>
</tr>
<tr>
<td>PUNLMP&lt;sup&gt;b&lt;/sup&gt;</td>
<td>Solitary LG Ta &gt; 3cm</td>
<td>Any recurrent, HG Ta</td>
</tr>
<tr>
<td></td>
<td>LG Ta, multifocal</td>
<td>HG Ta, &gt;3cm (or multifocal)</td>
</tr>
<tr>
<td></td>
<td>HG&lt;sup&gt;c&lt;/sup&gt; Ta, ≤ 3cm</td>
<td>Any CIS&lt;sup&gt;d&lt;/sup&gt;</td>
</tr>
<tr>
<td></td>
<td>LG T1</td>
<td>Any BCG failure in HG patient</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Any variant histology</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Any LVI&lt;sup&gt;e&lt;/sup&gt;</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Any HG prostatic urethral</td>
</tr>
<tr>
<td></td>
<td></td>
<td>involvement</td>
</tr>
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</table>

<sup>a</sup>LG = low grade; <sup>b</sup>PUNLMP = papillary urothelial neoplasm of low malignant potential; <sup>c</sup>HG = high grade; <sup>d</sup>CIS = carcinoma in situ; <sup>e</sup>LVI = lymphovascular invasion
Repeat TURBT

2016 AUA Guideline Recommendations

• Repeat TUR in any patient with incomplete resection
  (Strong Recommendation; Evidence Strength: Grade B)

• High risk, high grade Ta tumors consider repeat TUR within 6 weeks
  (Moderate Recommendation; Evidence Strength: Grade C)

• T1 Tumors, repeat TUR to include muscularis propria with 6 weeks
  (Strong Recommendation; Evidence Strength: Grade B)
Repeat TURBT

Randomized Trial Data

Number of pts recurring is HIGHER for NO Repeat TUR

Randomized T1 cohort of 210 patients

p = 0.0001

Goals of Intravesical Therapy

High local concentration directly to bladder tissue

• Adjuvant therapy to prevent recurrence and progression of disease

• Bladder Preservation
Intravesical Therapy

2016 AUA Guideline Recommendations

• Consider post administration of intravesical chemotherapy within 24 hrs of TURBT in suspected or known low-intermediate risk NMIBC

• Avoid in suspected perforation or extensive resection

(Strong Recommendation; Evidence Strength: Grade B)

Intravesical Therapy

2016 AUA Guideline Recommendations

• Do NOT administer induction intravesical therapy in low risk patient
  (Moderate Recommendation; Evidence Strength: Grade C)

• Consider 6 week induction course of intravesical chemotherapy or immunotherapy in intermediate risk patient
  (Moderate Recommendation; Evidence Strength: Grade B)

• Administer 6 week induction course of BCG for high risk patient (CIS, HGT1, HGTa)
  (Strong Recommendation; Evidence Strength: Grade B)
2016 AUA Guideline Recommendations

• Insufficient evidence to recommend a particular strain of BCG
  – Small studies suggest that different strains have different efficacies

• Insufficient evidence to prescribe a particular strength of BCG
  – EORTC 30962 recommends full dose for 3 years for High risk patients
  – No difference in recurrence free survival between full or 1/3 in low risk patients

• Insufficient evidence to use BCG in combination with other agents
  – Ongoing trials examining combination therapy
2016 AUA Guideline Recommendations

• Intermediate risk patient who completely responds to induction BCG should consider maintenance for 1 year
  (Moderate Recommendation; Evidence Strength: Grade C)

• High risk patient who completely responds to induction BCG should continue maintenance BCG for 3 years
  (Strong Recommendation; Evidence Strength: Grade B)
### BCG Maintenance

#### Events / Patients

<table>
<thead>
<tr>
<th></th>
<th>1 yr</th>
<th>3 yr</th>
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</thead>
<tbody>
<tr>
<td>1/3 dose – intermediate risk</td>
<td>106/192</td>
<td>97/218</td>
</tr>
<tr>
<td>Full dose – intermediate risk</td>
<td>72/191</td>
<td>81/188</td>
</tr>
<tr>
<td>1/3 dose – high risk</td>
<td>60/149</td>
<td>48/119</td>
</tr>
<tr>
<td>Full dose – high risk</td>
<td>73/146</td>
<td>49/146</td>
</tr>
<tr>
<td><strong>Total</strong></td>
<td>311/678</td>
<td>275/671</td>
</tr>
</tbody>
</table>

#### Statistics

<table>
<thead>
<tr>
<th></th>
<th>(O-E)</th>
<th>Var.</th>
<th>HR &amp; CI*</th>
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</thead>
<tbody>
<tr>
<td>1/3 dose – intermediate risk</td>
<td>15.2</td>
<td>50</td>
<td>1.35 (1.03; 1.79)</td>
</tr>
<tr>
<td>Full dose – intermediate risk</td>
<td>-4.8</td>
<td>38.2</td>
<td>0.88 (0.64; 1.21)</td>
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<tr>
<td>1/3 dose – high risk</td>
<td>0.2</td>
<td>28.6</td>
<td>1.01 (0.89; 1.47)</td>
</tr>
<tr>
<td>Full dose – high risk</td>
<td>14.4</td>
<td>30.2</td>
<td>1.61 (1.13; 2.30)</td>
</tr>
<tr>
<td><strong>Total</strong></td>
<td>25</td>
<td>145</td>
<td>1.19 (1.01; 1.40)</td>
</tr>
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#### Test for heterogeneity

Chi-square = 7.79, df = 3: p = 0.05

Treatment effect: p = 0.04
BCG Failure

BCG works well, but.......

- 40-50% with T1 disease will either fail to respond or relapse

- 15-20% will progress on BCG

- Disease Specific Survival: 70-85% @ 5 years

Slyvester et al. J Urol, 2005
Brake et al. Urology, 2000
BCG Failure Definition

- **BCG Refractory**: Failure to achieve a disease-free state by 6 months because of either persistent or rapidly recurrent disease.
  - Any progression in stage, grade, or disease extent by 3 months after first cycle of BCG

- **BCG Resistant**: Recurrence or persistence of disease at 3 months after the induction cycle. It is of lesser degree, stage, or grade, and is no longer present at 6 months

- **BCG Relapsing**: Recurrence of disease after achieving a disease-free status by 6 months
  - early (within 12 months)
  - intermediate (12 to 24 months)
  - late (> 24 months)

- **BCG Intolerant**: Recurrent disease in setting of inadequate BCG treatment because of drug toxicity

Nieder et al. Urology 66 (6A), 2005
BCG Failure

2016 AUA Guideline Recommendation

• **Intermediate-High Risk** patient with persistent or recurrent disease or positive cytology following intravesical therapy, consider prostatic urethra biopsy and upper tract imaging before giving additional intravesical therapy
  (Conditional Recommendation; Evidence Strength: Grade C)

• **Intermediate-High Risk** patient with persistent or recurrent Ta or CIS after single induction course of BCG should be offered second induction course
  (Moderate Recommendation; Evidence Strength: Grade C)

• **HGT1** disease after single induction course of BCG should be offered radical cystectomy if fit for surgery
  (Moderate Recommendation; Evidence Strength: Grade C)
Enhanced Imaging

• Narrow Band Imaging (NBI)
• Blue-Light Cystoscopy (Hexaminolevulinate-Cysview)
Narrow Band Imaging

Filters white light into 2 discrete short wavelength light beams

• Blue 415nm: Displays mucosal capillaries
• Green 540nm: Deeper sub-mucosal vessels
Narrow Band Imaging

- Enhances differentiation between lesion and normal mucosa
- Vasculature appears dark green/Black
Narrow Band Imaging

148 patients with NMIBC randomized to NBI-TUR vs. WL-TUR

<table>
<thead>
<tr>
<th></th>
<th>White Light</th>
<th>NBI</th>
<th>p value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Detection</td>
<td>1.36 lesions/patient</td>
<td>1.55 lesions/patient</td>
<td>0.07</td>
</tr>
<tr>
<td>3 mo recurrence</td>
<td>16.7%</td>
<td>3.9%</td>
<td>0.008</td>
</tr>
<tr>
<td>1 year recurrence</td>
<td>51.4%</td>
<td>31.6%</td>
<td>0.014</td>
</tr>
</tbody>
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Diagnosis of narrow-band imaging in non-muscle-invasive bladder cancer: A systematic review and meta-analysis

Kaiwen Li,1,2* Tianxin Lin,1,2* Xinxiang Fan,1,2* Yu Duan3 and Jian Huang1,2

- Meta-analysis of 7 studies
- N=1080 pts with 1476 tumors

- 24% additional tumors detected by NBI
- 28% additional CIS detected by NBI
- No difference in false positive rate

Study that led to FDA approval
Fluorescence Cystoscopy

FDA approve in 2010

• Photosensitizing agent (Hexaminolevulanic Acid) instilled into bladder via catheter
  – Interferes with Heme biosynthesis pathway

• Intracellular accumulation of photoactive porphyrins (rapidly proliferating cells)

• Blue light illumination (380nm-440nm): Tumor cells fluoresce red
Fluorescence Cystoscopy

- 286 patients: Ta or T1
  - Randomized to white light or white light and blue light
- Additional Tumors detected with blue light
  - Ta: 16%
  - T1: 13%
  - CIS: 46%
- CIS only: 41 pts
  - 32% only seen with blue light
- No difference in false positives

Stenzl et al. J Urol. 2010
Fluorescence Cystoscopy

- Tumor recurrence rates over 9 months
  - Blue Light: 47%
  - White Light: 56% \( (p = 0.026) \)
- Relative reduction in recurrence rate was 16% with blue light cystoscopy

Stenzl et al. J Urol. 2010
2016 AUA Guideline Recommendations

• Blue light cystoscopy should be offered if available at the time of TURBT to increase detection and decrease recurrence
  (Moderate Recommendation; Evidence Strength: Grade B)

• Narrow Band Imaging can be considered to increase detection and decrease recurrence in NMIBC
  (Conditional Recommendation; Evidence Strength: Grade C)
Variant Histology

2016 AUA Guideline Recommendations

• GU pathology review for any doubt of variant or suspected variant histology (micropapillary, nested, plasmacytoid, neuroendocrine, sarcomatoid)
  (Moderate Recommendation; Evidence Strength: Grade C)

• Restage TURBT within 4-6 weeks if considering bladder sparing approach in variant histology
  (Expert Opinion)

• Consider Cystectomy in variant histology due to high rate of upstaging
  (Expert Opinion)
Variant Histology

Radical Cystectomy
Role of Cystectomy

2016 AUA Guideline Recommendations

• Should not preform cystectomy until bladder sparring therapies have failed in Ta low-intermediate risk disease

  (Clinical Principle)

• Initial radical cystectomy should be considered in high risk patient fit for surgery with persistent T1 disease, T1 + CIS, LVI, or variant histology

  (Moderate Recommendation; Evidence Strength: Grade C)

• Offer cystectomy in high risk patient with persistent or recurrent disease within one year of receiving two induction cycles of BCG

  (Moderate Recommendation; Evidence Strength: Grade C)
Role of Cystectomy

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  (Moderate Recommendation; Evidence Strength: Grade C)
Radical Cystectomy

• Cures >90% done before progression to muscle invasive disease

• Survival worse for progression to muscle invasive disease after BCG vs primary muscle invasive disease - 3 yr DSS: 37% vs 67%
  Van Den Bosch et al. Eur Urol 2011

• Delay of Cystectomy affects survival
  – 5 year CSS: 80% vs 69%
  – 10 year CSS: 76-78% vs 51-61%

• Mean time to Cystectomy NMIBC
  Guzzo et al. Urol 2009
  – No BCG: 5.5 months
  – With BCG: 20.1 months
Radical Cystectomy

? Default Treatment
- Patient preference for bladder preservation

- 90d mortality of 10% in elderly population (Pycha et al. Expert Rev Anticancer Ther 2011)

- Competing morbidity
  - Complication rate of 30-70% (Shabsigh et al. Eur Urol. 2009)

- Overtreatment
  - Viable therapies for bladder preservation
Radical Cystectomy

Gupta et al. Urol. 2008
“Patients with recurrent nonmuscle invasive disease underwent cystectomy only when high grade tumors were not eradicated by vigorous intravesical treatment and serious bladder symptoms were attributable to local disease”

- N = 35
- Early Cystectomy: Within 2 years Median 11 mos (3-23) DSS: 92%
- Delayed Cystectomy: > 2 years Median 55 mos (25-228) DSS: 56%
2016 AUA Guidelines

Take Home Messages

• Risk Adjusted Treatment Recommendations
• Repeat TURBT within 6 weeks for high risk patients
• Risk Adjusted BCG Maintenance Protocols
• New technology for better detection
• Cystectomy: Highest risk patients
Thank you

Trushar Patel, M.D.