Management of High-Risk Non-Muscle Invasive Bladder Cancer

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

Objectives:

- Discuss optimal strategy for determination of stage and grade and extent of the cancer
- Review application of newer methods of endoscopic imaging that complement white light cystoscopy
- Critique risk stratification and appropriate individualized disease management
- Evaluate strategies for minimizing and managing complications of intravesical therapy
- Apply appropriate decision making regarding the use of salvage intravesical therapy
Management of High Risk Non Muscle Invasive Bladder Cancer

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

• Laboratory research
  – Celgene, Cephalon

• Clinical trials
  – NCI, Endo, FKD, Imalux, Tengion

• Advisory Board
  – Imalux, Photocure, Taris, Tengion

• Consultant
  – BioCancell, Dendreon, Physion, Theracoat, Vaxiion
Goals and Objectives

• Understand optimal strategy for determination of stage and grade and extent of the cancer
• Application of newer methods of endoscopic imaging that complement white light cystoscopy
• Risk stratification and appropriate individualized disease management
• Strategies for minimizing and managing complications of intravesical therapy
• Apply appropriate decision making regarding the use of salvage intravesical therapy
• **Low** - TaG1 solitary, primary, < 3cm - 50% patients

• **Intermediate** - Multifocal, recurrent TaT1, G1-2, 35% patients

• **High** - CIS, any G3(Ta or T1) - 15% of patients

EAU Guidelines 2013
## Risk Stratification

### Recurrence and Progression Risk

<table>
<thead>
<tr>
<th>Risk group</th>
<th>Recurrence (%)</th>
<th>Progression (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>1yr</td>
<td>5yr</td>
</tr>
<tr>
<td>Low</td>
<td>15</td>
<td>31</td>
</tr>
<tr>
<td>Intermediate</td>
<td>24-38</td>
<td>46-62</td>
</tr>
<tr>
<td>High</td>
<td>61</td>
<td>78</td>
</tr>
</tbody>
</table>
### EORTC Risk Tables for Stage Ta T1 Bladder Cancer

<table>
<thead>
<tr>
<th>Prior Recurrence Rate</th>
<th>Number of Tumors</th>
<th>Tumor Diameter</th>
<th>T Category</th>
<th>Grade (WHO 1973)</th>
<th>Concomitant CIS</th>
</tr>
</thead>
<tbody>
<tr>
<td>Primary</td>
<td>1</td>
<td>&lt; 3 cm</td>
<td>Ta</td>
<td>G1</td>
<td>No</td>
</tr>
<tr>
<td>Recurrent &lt;= 1 per year</td>
<td>2 to 7</td>
<td>&gt;= 3 cm</td>
<td>T1</td>
<td>G2</td>
<td>Yes</td>
</tr>
<tr>
<td>Recurrent &gt; 1 per year</td>
<td>8 or more</td>
<td></td>
<td></td>
<td>G3</td>
<td></td>
</tr>
</tbody>
</table>

#### Calculate Probabilities

<table>
<thead>
<tr>
<th></th>
<th>1 Year</th>
<th>2 Years</th>
<th>3 Years</th>
<th>4 Years</th>
<th>5 Years</th>
</tr>
</thead>
<tbody>
<tr>
<td>Probability of Recurrence</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Probability of Progression</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>


Programmed by Richard Sylvester, EORTC Data Center, 83 avenue Mounier, 1200 Brussels, Belgium.

Version 1.0, January 2006

Sylvester et al Eur Urol 49:466, 2006
http://www.eortc.be/tools/bladdercalculator
High Risk NMIBC

*Predictors of Understaging*

- Incomplete TUR
- No muscle in the TUR specimen
- Multifocal or large lesions
- Associated carcinoma in situ
- Lymphovascular invasion
- Mass on bimanual exam
- Hydronephrosis
- Prostatic urethra involvement
Case 1

- 61 yo male with gross hematuria
- TURBT T1HG
- *No re-resection; No BCG*
- 5 months later cytology and FISH normal
- *15 mos later T1HG – no re-resection*
- Now treated with BCG induction only
- 29 mos from first diagnosis T2HG – needs cystectomy
Transurethral Resection of Invasive Bladder Tumor

EAU Guidelines: Without the presence of muscularis propria the pathologist is unable to stage as Ta, T1 or T2

Herr, TURBT 2006
Re-TUR T1 – Randomized Clinical Trial


Number of pts recurring in each group

 Survival Functions for Recurrence

<table>
<thead>
<tr>
<th>Cum Survival</th>
<th>RFS (mo)</th>
</tr>
</thead>
<tbody>
<tr>
<td>0.0, 0.2, 0.4, 0.6, 0.8, 1.0</td>
<td>0, 20, 40, 60, 80, 100</td>
</tr>
</tbody>
</table>

p = 0.0001
Re-TUR T1 – Randomized Clinical Trial


Number of pts recurring in each group

p = 0.0001
Re-Resection for High Grade T1

• EAU guidelines
  – 2–6 wk after the initial resection when aT1 tumor is detected

• AUA guidelines
  – All patients with T1

• NCCN guidelines
  – “Strongly advise”

• ICUD
  – “Warranted”
Indications for Site Directed Biopsies

- Purpose to identify non-visible CIS
- Unexplained positive cytology
- Suspicion of and/or history of CIS
- High grade disease
- *Evaluate extravesical sites with high grade recurrence*
  - *Upper tracts and prostatic urethra – CIS reservoir*
Staging Prostatic Urethra

- BCG treatment failed in 62 high-risk cases; patients underwent cystectomy
- Prostatic urethra TCC most important predictor of muscle-invasive cancer
  - Hazard ratio, 12.2 (2.2-65.5) \( P = .003 \)
- Sampling from the urethra in high-risk patients is essential

Risk Adapted Treatment

• Low risk – *Ta* low grade solitary, primary, < 3cm
  – Peri-operative chemotherapy only

• Intermediate risk - *Multifocal, recurrent Ta, T1 low grade*
  – Peri-op plus induction chemotherapy ± maintenance
  – BCG is an option

• High Risk – *CIS, Ta, T1 high grade*
  – Peri-op no benefit
  – Induction BCG plus maintenance
Optimal use of BCG for Non-Muscle Invasive Bladder Cancer
Case 2

- 64 yo female
- 3cm tumor right lateral wall inside BN 7-11 o’clock
- Completely resected
- Path: T1G3 muscularis propria not involved
- Normal bimanual exam
- Re-resection no residual cancer and no CIS
BCG Indications

• Any patient with high risk NMIBC
  – TaHG, T1, Tis
• First occurrence – standard of care
• Recurrent
  – BCG naïve
  – BCG failure if no indication for cystectomy or medically unfit
• FDA approved for CIS and high risk Ta,T1
BCG Immunotherapy

• Is a single 6 week induction course of BCG adequate therapy?
• Should all patients receive maintenance BCG?
  – What is optimal duration?
• Is low dose BCG as effective?
• Is there a role for intravesical interferon?
  – BCG naïve
  – Salvage therapy
  – Interferon not FDA approved for bladder cancer
• 6-week induction course superior to TURBT alone for Ta, T1 and CIS (Level 1A)
  – Initial CR - 50-70%
• Second 6-week course $^{1,2}$ (Level 3)
  – Salvage additional 10-22%

BCG vs. Epirubicin - EORTC 30906 - CIS

- A second induction course of either drug achieved additional complete responses

<table>
<thead>
<tr>
<th>Table 3. Response to treatment</th>
</tr>
</thead>
<tbody>
<tr>
<td>Response</td>
</tr>
<tr>
<td>---------</td>
</tr>
<tr>
<td>CR:</td>
</tr>
<tr>
<td>Overall</td>
</tr>
<tr>
<td>After course 1</td>
</tr>
<tr>
<td>Partial response</td>
</tr>
<tr>
<td>No change</td>
</tr>
<tr>
<td>Progression</td>
</tr>
<tr>
<td>Unknown</td>
</tr>
<tr>
<td>Total</td>
</tr>
</tbody>
</table>

• Maintenance therapy rationale
  – Repeated stimulation of immune system
  – Can give too much BCG - cytokine response with second 6 week course peaks by week three and may be suppressed during weeks 4-6

• Maintenance BCG improves RFS and PFS (level 1B)
Urinary IFN-γ Response to Adding IFN-α and Decreasing BCG

BCG Response

1/3 BCG +IFN-α

1/10 BCG +IFN-α

IFN-γ (ng/12 hrs)
Urinary IL-8 levels

Thalmann et al., J Urol 1997
Kummar et al., J Urol 2002
Sagnak et al., Clin Genitourin Cancer 2009

(Courtesy George Thalmann)
Fluorescence in situ hybridization


(Faculty George Thalmann)
BCG - Facts

• CIS ± Ta, T1 (SWOG 8507) (Level 1B)
  – 3 month CR with Induction alone 56%
  – 6 month CR with Induction alone 68%
  – 6 month CR 6 +3 84%

• Full dose BCG + 3 yrs maintenance optimal therapy for high risk disease (EORTC 30962) (Level 1B)

• BCG superior to MMC (Level 1A) and Epirubicin (Level 1B) only when maintenance therapy used\(^1,^2\)

\(^1\) Sylvester, et al J Urol 174:86, 2005
### Maintenance BCG - SWOG 8507

<table>
<thead>
<tr>
<th>Month</th>
<th>0</th>
<th>3</th>
<th>6</th>
<th>9</th>
<th>12</th>
<th>15</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cysto</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
</tr>
<tr>
<td>BCG</td>
<td>6</td>
<td>3</td>
<td>3</td>
<td>3</td>
<td>3</td>
<td></td>
</tr>
<tr>
<td>Month</td>
<td>18</td>
<td>21</td>
<td>24</td>
<td>30</td>
<td>36</td>
<td></td>
</tr>
<tr>
<td>Cysto</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
</tr>
<tr>
<td>BCG</td>
<td>3</td>
<td>3</td>
<td>3</td>
<td>3</td>
<td>3</td>
<td></td>
</tr>
</tbody>
</table>
SWOG 8507 - Recurrence-Free Survival

Lamm, DL et al, J Urol 163:1124, 2000

p < 0.0001

<table>
<thead>
<tr>
<th>Maintenance</th>
<th>N</th>
<th>Events</th>
<th>Median</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>192</td>
<td></td>
<td>77</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>No Maintenance</th>
<th>N</th>
<th>Events</th>
<th>Median</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>192</td>
<td></td>
<td>36</td>
</tr>
</tbody>
</table>
SWOG 8507 – Worsening-Free Survival

Lamm, DL et al, J Urol 163:1124, 2000

p = 0.04
Status at 3 month cystoscopy associated with outcome

Unadjusted Survival Curves by CR Status During Induction

• Assess the response to BCG 3 mos after starting treatment.
  – If no response, options are cystectomy, repeat 6 (re-induction) or 3 wks (maintenance) BCG

• Progression risk
  – 10-20% of responders
  – 66% of non-responders !!!!!

• The optimal time to abandon conservative treatment and proceed to cystectomy is unknown.

Level of evidence 2b, Grade B recommendation

EAU / ICUD Eur Urol 2012
NCCN
Post BCG - Should I Biopsy?

- 180 high risk patients post induction BCG
- All with cysto, cytology and biopsy
- 32% with positive biopsy
- 35% of patients had nl cysto and normal cytology
  - 94% had a negative biopsy
- Meta Analysis (6 studies)
  - PPV erythematous lesion (25%), tumor (76%) and positive cytology (51%)

PDD Post BCG

• 27 patients; 32 fluorescence cysto with hexyl-aminolevulinic acid (HAL)
• Days since BCG: 59 (29-226)
• Recurrent cancer 11/32 (34%)
  – 5 (19%) patients detected with HAL alone
• False positive biopsy 63% (34% with positive cytology)
  – Independent of time since BCG

Ray, et al BJUI 2009
Caveats From SWOG 8507

- Recurrence probability at 10 years exceeded 70%
  - Lifelong follow-up required
- Only 16% completed 36 months of therapy
- 278 patients with CIS

<table>
<thead>
<tr>
<th></th>
<th>Complete response</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>n</td>
</tr>
<tr>
<td>No maintenance</td>
<td>116</td>
</tr>
<tr>
<td>Maintenance</td>
<td>117</td>
</tr>
</tbody>
</table>

Lamm, DL et al, J Urol 163:1124, 2000
BCG - Facts

• Can re-induce CR with BCG in late relapsers (> 1 year)
• Randomized phase II trials to date testing a second induction course of BCG alone in patients who have failed one induction course
  — 2 yr RFS 3% vs. 19% for Gemcitabine (Level 2B)\(^1\)
• Patients with CIS who have failed 2 courses of BCG should not be treated with a 3\(^{rd}\) course (Level 2B)\(^2\)

\(^1\) Di Lorenzo et al Cancer 116:1893, 2010
\(^2\) Rosevear, JUrol 186:817, 2011
CIS – When is Cystectomy Indicated?

• Diffuse involvement of bladder
• Patient will not tolerate BCG or contraindicated
• Failed two induction course of BCG or BCG 6+3
• T1G3 + CIS
• Extravesical sites
  – Intramural ureter
  – Prostatic urethra
Cancer Survival for CIS Patients

After BCG + IFN-α Treatment

Fraction Free of Cancer

Months After Treatment Initiation

BCG + IFN for BCG Naïve Patients

- Randomization 1:1:1:1
  - BCG (Tice)
  - BCG 1/3 + IFN 50 mil u
  - RDA vitamins
  - Oncovite
- Induction + maintenance 3 weekly at 7, 13, 19, 25 and 37 months
- 670 patients
  - CIS (8%)
  - G3-4 (20%)

No benefit to combination therapy

Take Home Message

• High risk disease – any high grade Ta or T1 and any CIS
  – BCG standard of care
  – Maintenance therapy improves recurrence and progression-free survival
  – No role for Interferon in BCG naïve patients
    • May be beneficial as salvage therapy
BCG Dose Reduction

• Sometimes less is better
• An appropriate cytokine response can be achieved with as little as 1/100 of a standard dose
• Dose reduce in face of toxicity rather than abandon potentially effective therapy – 1/2, 1/3, 1/10, 1/30, 1/100
EORTC 30962

- Dose reduction
- Short (3, 6, 12 mos.) vs. long-term (3 years) maintenance
- Intermediate and high risk Ta, T1
- 4 arms
  - BCG standard dose + long-term maintenance
  - BCG 1/3 dose + long-term maintenance
  - BCG standard dose + short-term maintenance
  - BCG 1/3 dose + short-term maintenance

EORTC 30962

- No significant increase in toxicity with 3 years vs. one year
- Study did not meet pre-defined endpoint of 10% difference in recurrence rate (RR)
- There was a difference in RR at the extremes – 1 year vs. 3 year
- Full Dose-3yrs had the highest Disease Free rate at 5 yrs while 1/3 Dose-1yr had the lowest
• Is a single induction course of BCG adequate therapy? - No
• Should all patients receive maintenance BCG? - Yes
• Is less BCG as effective? - Sometimes
• Has interferon become “standard therapy”? – No
• Should interferon be used only after failure of induction BCG? – Yes, for now
Algorithm

Induction BCG – weekly x 6

6 weeks

Cysto, cytology ± Biopsy

CR

BCG weekly x 3

CR

pos cytology

BCG maint SWOG 8507

PR

BCG weekly x 3 or weekly x 6

CR

pos cytology

BCG maint SWOG 8507

NR

Cystectomy

CR

pos cytology

BCG maint SWOG 8507

BCG±IFN maint SWOG 8507

CR

PR

NR

Biopsy

Biopsy

Biopsy

Cystectomy

NR

SWOG 8507

SWOG 8507

SWOG 8507

SWOG 8507

CR: neg cysto/cytology
PR: neg cyto/+ cytology
NR: + biopsy
When BCG Fails the Patient

- Valrubicin – only FDA approved drug
- Gemcitabine
- Optimized MMC
- Gem/MMC
- BCG/IFN
- Clinical trial
# Cystectomy Indications CIS

## Guideline Recommendations

<table>
<thead>
<tr>
<th></th>
<th>Primary CIS</th>
<th>T1 + CIS</th>
<th>Failed BCG x 1</th>
<th>Failed BCG x 2</th>
<th>Prostatic urethra</th>
<th>Prostatic ducts/aci ni</th>
</tr>
</thead>
<tbody>
<tr>
<td>AUA</td>
<td>Option</td>
<td>Option</td>
<td>✓</td>
<td>✓</td>
<td>Option</td>
<td>10</td>
</tr>
<tr>
<td>EAU</td>
<td>X</td>
<td>✓</td>
<td>----</td>
<td>✓</td>
<td>✓</td>
<td>10</td>
</tr>
<tr>
<td>ICUD</td>
<td>✓</td>
<td>✓</td>
<td>X</td>
<td>✓</td>
<td>✓</td>
<td>10</td>
</tr>
<tr>
<td>NCCN</td>
<td>X</td>
<td>✓</td>
<td>X</td>
<td>✓</td>
<td>X</td>
<td>✓</td>
</tr>
</tbody>
</table>