Overview of Diagnosis and Management of Non-Muscle Invasive Bladder Cancer

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

ODAC September 14, 2016
Disclosures

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

• Advisory Board
  – Ferring, Nucleix, OncoGeneX, Sitka, Taris

• Consultant
  – Biocancell, Telesta, Theracoat, Vaxiion
Overview

• Bladder cancer statistics
• Staging and grading NMIBC
• Risk stratification and treatment according to risk strata
• Outcomes: recurrence vs. progression
• Differences in population, disease management, US vs. Canada vs. Poland
• Current state of the art for peri-op chemo
• 76,960 new cases
• 16,390 deaths
  – 77.5% 5 year survival (2006-2012)
• 89% of U.S. patients ≥ 55 years old
• 4th most common cancer in men
  – Prostate, lung, colorectal more common
• 10th most common solid tumor cancer in women
• U.S. Prevalence 587,246 (SEER, 2013)
  – Lifetime risk 2.4%
• Cost per patient: Most expensive cancer from diagnosis to death

Are There Geographic Differences

- Poland – follow EAU guidelines

**Figure 6.5. The structure of registered cancer incidence, males, Poland 2013**

<table>
<thead>
<tr>
<th>Cancer Site</th>
<th>Percentage</th>
</tr>
</thead>
<tbody>
<tr>
<td>Lung (C33+C34)</td>
<td>18.7%</td>
</tr>
<tr>
<td>Grucoł krokowy (Prostate)</td>
<td>15.5%</td>
</tr>
<tr>
<td>Jelito grube (Colorectum)</td>
<td>12.2%</td>
</tr>
<tr>
<td>Pęcherz moczyowy (Urinary bladder)</td>
<td>6.9%</td>
</tr>
<tr>
<td>Żołądek (Stomach)</td>
<td>4.5%</td>
</tr>
<tr>
<td>Nerka (Kidney)</td>
<td>4.0%</td>
</tr>
<tr>
<td>Białaczki (Leukeamias)</td>
<td>2.5%</td>
</tr>
<tr>
<td>Krtań (Larynx)</td>
<td>2.4%</td>
</tr>
<tr>
<td>Trzustka (Pancreas)</td>
<td>2.3%</td>
</tr>
<tr>
<td>Chłoniaki (C82–C85+C96) (Lymphomas)</td>
<td>2.0%</td>
</tr>
<tr>
<td>Umiejscowienie nieokreślone NOS (C76+C80)</td>
<td>1.5%</td>
</tr>
</tbody>
</table>

**Figure 6.6. The structure of registered cancer incidence, females, Poland 2013**

<table>
<thead>
<tr>
<th>Cancer Site</th>
<th>Percentage</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pierś (Breast)</td>
<td>21.9%</td>
</tr>
<tr>
<td>Jelito grube (Colorectum)</td>
<td>10.1%</td>
</tr>
<tr>
<td>Płuco (Lung) (C33+C34)</td>
<td>8.8%</td>
</tr>
<tr>
<td>Trzon macicy (Corpus uteri)</td>
<td>7.3%</td>
</tr>
<tr>
<td>Jajnik (Ovary)</td>
<td>4.7%</td>
</tr>
<tr>
<td>Szyjka macicy (Cervix uteri)</td>
<td>3.7%</td>
</tr>
<tr>
<td>Tarczyca (Thyroid gland)</td>
<td>2.9%</td>
</tr>
<tr>
<td>Nerka (Kidney)</td>
<td>2.6%</td>
</tr>
<tr>
<td>Żołądek (Stomach)</td>
<td>2.4%</td>
</tr>
<tr>
<td>Trzustka (Pancreas)</td>
<td>2.2%</td>
</tr>
<tr>
<td>Umiejscowienie nieokreślone NOS (C76+C80)</td>
<td>1.7%</td>
</tr>
</tbody>
</table>

Roman Sosnowski, personal communication
Clinical and Pathologic Tumor Staging

- Fat
- Muscle
- Connective tissue
- Bladder lining

- CIS
- Ta
- T1
- T2
- T3
- T4

Grading of Papillary Lesions

- **WHO 1973**
  - G1 – well differentiated
  - G2 – Moderately differentiated
  - G3 – Poorly differentiated

- **WHO/ISUP 1998**
  - Low grade
  - High grade

- **WHO 2004**
  - Identical to WHO/ISUP 1998
Relationship of 1973 WHO to 2004 WHO/ISUP

<table>
<thead>
<tr>
<th>WHO 1973</th>
<th>WHO 2004</th>
</tr>
</thead>
<tbody>
<tr>
<td>Papilloma</td>
<td>Papilloma</td>
</tr>
<tr>
<td>Grade 1</td>
<td>PUNLMP</td>
</tr>
<tr>
<td>Grade 2</td>
<td>Low grade</td>
</tr>
<tr>
<td>Grade 3</td>
<td>High grade</td>
</tr>
</tbody>
</table>

Eur Urol 46:170, 2004

www.pathology.jhu.edu/bladder
WHO 1973 and 2004 WHO/ISUP Grade

Recurrence

Progression

Pathologic, Morphologic and Clinical Features

• Accurate determination of stage and grade
  – Surgical quality – TURBT and bladder biopsies
  – *Strongly* recommend re-review and 2\(^{nd}\) TUR for T1G3

• Variant histology: micropapillary

• Focality – single vs. multiple

• Presence of CIS

• Status at 3 month follow-up

• Tumor size
Risk Stratification – EAU

- **Low** – Ta low grade solitary, primary, ≤ 3cm - 50% patients
- **Intermediate** - Multifocal, recurrent Ta, low grade, ≤3cm - 35% patients
- **High** - CIS, any high grade (Ta or T1); multifocal and recurrent and >3cm TaLG – 15%
- **Very high** - Multiple and/or large (>3 cm) T1HG, T1HG + CIS ± P urethra, micropapillary

EAU Guidelines 2016 (updated)
Risk Stratification – AUA/SUO

- **Low** – TaLG solitary, primary, $\leq 3\text{cm}$; PUNLMP
- **Intermediate** – TaLG $> 3\text{cm}$; Recurrence, 1 year; multifocal, recurrent Ta, low grade, $\leq 3\text{cm}$; High grade Ta HG $\leq 3\text{cm}$; T1 LG
- **High** – T1 HG; any recurrent TaHG; Ta HG $> 3\text{cm}$ or multifocal; CIS; any recurrence after BCG; any variant histology or LVI; any high grade cancer in prostatic urethra
<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>

NB. Based largely on randomized trials of intravesical chemotherapy

EORTC risk Calculator Eur Urol 49:466, 2006
Risk Adapted Treatment

- **Low** – peri-operative chemotherapy only
- **Intermediate** – peri-op plus induction chemotherapy ± maintenance
- **High** – peri-op plus induction BCG plus maintenance
  - Assess response with cysto, cytology, and biopsy (for CIS)
- **Very high** – consider primary cystectomy
# Intravesical Immunotherapy and Chemotherapy

## Immunomodulatory agents
- **Bacillus Calmette-Guérin (BCG)**
  - Approved for Ta, T1HG and CIS
- **Interferons**

## Mechanism of Action
- Inflammatory host response; release of cytokines
- May be combined with interferons
- Lymphocyte activation; cytokine release; phagocyte stimulation
- Antiproliferative actions
- Antiangiogenic

## Chemotherapeutic Agents
- **Thiotepa**
  - Approved for superficial papillary
- **Mitomycin C**
- **Doxorubicin, epirubicin, valrubicin**
  - Val approved for BCG refractory CIS
- **Gemcitabine**

AUA Guidelines
Guidelines and Treatment of NMIBC

- Peri-operative single dose chemotherapy
  - TaLG only (AUA, NCCN, EAU)
  - All patients with NMIBC (CUA, NICE)

- Induction intravesical chemotherapy +/- 1 year maint
  - Intermediate risk
  - Induction alone (AUA, NCCN, NICE)
  - Induction + maint (EAU, CUA)

- Induction BCG + maintenance 3 yr
  - All high risk patients

- Radical cystectomy
  - Option for highest risk patients and BCG unresponsive

Power and Izawa, Bladder Cancer 2:27, 2016
Special Report  


Jonathan P. Jarow, Seth P. Lerner, Paul G. Klco, Dean Bajorin, Sam Chang, Colin P. N. Dinney, Michael O’Donnell, Diane Zipursky Quale, Mai Bhadrasain Vikram

DOI 10.3233/BLC-159002
IOS Press

Short Communication  

Clarification of Bladder Cancer Disease States Following Treatment of Patients with Intravesical BCG

Development of Systemic and Topical Drugs to Treat Non-muscle Invasive Bladder Cancer

Jonathan Jarow, a V. Ellen Maher, a Shenghui Tang, c Amna Ibrahim, b Geoffrey Kim, b Rajeshwari Sridhara, a and Richard Pazdur b
Case

- 60-year-old woman
- Gross painless hematuria x 6 months
- Multiple courses of antibiotics

Solitary LG Ta tumor
Low risk disease
Post-TUR Drug Options

Options:
- Mitomycin C  30-40 mg in 20-50cc
- Doxorubicin  40-50 mg in 50cc
- Epirubicin   80 mg in 50cc
- Gemcitabine  2gms in 100cc (SWOG 0337 report due 2016)

• Retain x 1-2 hours
• Options:
  – Treat in OR or PAR
  – Ideal to treat within first 6-24 hours post-TUR

➤ **DO NOT DO** in face of possible perforation
➤ **NEVER use BCG** post-TUR
Post-TUR Epirubicin

214 patients epirubicin vs. no instillation
Most helpful for lowest risk tumors:

Rare Toxicities

Dystrophic calcification of the bladder following Mitomycin C

Ulcer in buccal mucosa following cutaneous Gemcitabine absorption
### Post-TUR Chemotherapy – Systematic Review

<table>
<thead>
<tr>
<th>Study or Subgroup</th>
<th>log[Hazard Ratio]</th>
<th>SE</th>
<th>Weight</th>
<th>Hazard Ratio IV, Random, 95% CI</th>
<th>Year</th>
</tr>
</thead>
<tbody>
<tr>
<td>Oosterlinck</td>
<td>-0.4108</td>
<td>0.176</td>
<td>10.3%</td>
<td>0.66 [0.47–0.94]</td>
<td>1993</td>
</tr>
<tr>
<td>MRC</td>
<td>0.1044</td>
<td>0.1834</td>
<td>10.1%</td>
<td>1.11 [0.77–1.59]</td>
<td>1994</td>
</tr>
<tr>
<td>Fujita</td>
<td>-0.654</td>
<td>0.343</td>
<td>6.0%</td>
<td>0.52 [0.27–1.02]</td>
<td>1994</td>
</tr>
<tr>
<td>Tolley</td>
<td>-0.415</td>
<td>0.1632</td>
<td>10.7%</td>
<td>0.66 [0.48–0.91]</td>
<td>1996</td>
</tr>
<tr>
<td>Solsona</td>
<td>-0.346</td>
<td>0.1821</td>
<td>10.1%</td>
<td>0.71 [0.50–1.01]</td>
<td>1999</td>
</tr>
<tr>
<td>Okamura</td>
<td>-1.17</td>
<td>0.304</td>
<td>6.8%</td>
<td>0.31 [0.17–0.56]</td>
<td>2002</td>
</tr>
<tr>
<td>Rajala</td>
<td>-0.742</td>
<td>0.231</td>
<td>8.7%</td>
<td>0.48 [0.30–0.75]</td>
<td>2002</td>
</tr>
<tr>
<td>Berrum-Svennung</td>
<td>-0.348</td>
<td>0.1521</td>
<td>11.1%</td>
<td>0.71 [0.52–0.95]</td>
<td>2008</td>
</tr>
<tr>
<td>Gudjonsson</td>
<td>-0.4</td>
<td>0.1635</td>
<td>10.7%</td>
<td>0.67 [0.49–0.92]</td>
<td>2009</td>
</tr>
<tr>
<td>Bohle</td>
<td>-0.051</td>
<td>0.1979</td>
<td>9.7%</td>
<td>0.95 [0.64–1.40]</td>
<td>2009</td>
</tr>
<tr>
<td>De Nunzio</td>
<td>-1.61</td>
<td>0.3504</td>
<td>5.8%</td>
<td>0.20 [0.10–0.40]</td>
<td>2011</td>
</tr>
</tbody>
</table>

**Total (95% CI):**

<table>
<thead>
<tr>
<th>Weight</th>
<th>Hazard Ratio IV, Random, 95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>100.0%</td>
<td>0.62 [0.50, 0.77]</td>
</tr>
</tbody>
</table>

Heterogeneity: Tau² = 0.09; chi-square = 31.97, df = 10 (p = 0.0004); I² = 69%

Test for overall effect: Z = 4.29 (p < 0.0001)

### 38% relative risk reduction

Previous meta analysis –11% absolute risk reduction for recurrence

Post-TUR Chemotherapy - Meta-analysis

• Individual patient data 11 of 13 trials
• N = 2278
• Relative risk reduction for recurrence 35%
  – HR 0.65 (0.58-0.74; p < 0.001)
• 5-year recurrence probability reduced from 58.8% to 44.8%
• No benefit in patients with > 1 recurrence/year or EORTC risk score ≥ 5
• No benefit for risk of progression or death

Post-TUR Chemotherapy - Meta-analysis

Time to First Recurrence

Stratified (study), p < 0.001

• Est 2-yr RR in control arm 60%
• Powered to detect 45% RR in Gem arm
• HR 1.53

**Primary objective:** Determine efficacy after transurethral bladder resection (TURBT) of single intravesical gemcitabine instillation versus saline instillation in preventing recurrence of completely resected Grade 1 or 2, Ta or T1 transitional cell cancer (TCC) of the bladder at two years.
Utilization and Judicious Use - US

• Survey of 259 US urologists\textsuperscript{1}
  – 61% participated
  – 1010 eligible patients
  – 17% received peri-op instillation
  – 66% of urologists never used

• Judicious use \textsuperscript{2}
  – Prospective quality improvement collaborative
  – 2794 patients over 22 months/5 practice sites
  – Ideal use 38% to 35% after intervention
  – Judicious use 83 to 86% (appropriate use and non-use)

\textsuperscript{1}Cookson, et al J Urol 187:1571, 2012
Utilization Peri-op CTX in Europe

• 324 urologists surveyed (France, Germany, Italy, Spain, UK)
  – 55% participated
  – 954 TURBT in 771 patients
  – 43% received peri-op CTx
  – Factors associated with utilization
    • Country (UK highest, France lowest), fellowship trained, higher risk for recurrence, lower risk of progression, higher volume NMIBC treated

Utilization Peri-op CTX in Canada

• Similar issues regarding low utilization as US
• Cost MMC 6 x Epirubicin so come centers using Epi preferentially
• Logistic constraints in high throughput operating room and managing cytotoxic ctx
• Small TaLG tumors often managed with office fulgeration
• Most care provided by community urologists
  – Centralized care to academic center only in one region in Quebec

Peter Black, Wassim Kasouf, personal communication
Summary – Peri-operative CTx

- Low and intermediate risk most appropriate
  - Solitary and multifocal and/or recurrent TaLG
  - Small volume TaHG
  - Safety proven but rare severe toxicities with MMC

- Utilization varies but increased from early reports

- Geographic variation in utilization within US, Canada and Europe

- But, guidelines consistent in recommending use