Radical Cystectomy: Optimizing Outcomes

- “Timely” cystectomy for T1, TaHG, CIS
- Quality of radical cystectomy
- Extended pelvic lymphadenectomy
- Peri-operative systemic therapy
- Improve morbidity and quality-of-life
High-Risk, Non-Muscle-Invasive Bladder Cancer*:
15-Year Outcomes with BCG

- 50% progression
- 34% mortality from bladder cancer
- 36% cystectomy rate
- 27% alive with bladder intact

- Median time to progression: 10 years

- 86 pts with high-risk superficial bladder cancer treated on RCT of BCG vs. observation, median FU 184 months, 86% received BCG

*Defined as T1 or CIS or TaHG

Cookson et al. J Urol 1997
Natural History: 15-Year Outcome

Cookson et al. *J Urol* 1997

SWOG 8507 Lamm et al. *J Urol* 2000
High-Risk, Non-Muscle-Invasive Bladder Cancer

- Carcinoma *in situ*
- T1, any grade
- Ta, high-grade

**Associated risk factors:**
- Size, multifocality, associated CIS, prostatic urethral involvement
- Prior bladder cancer history

**Patient factors:**
- Age, comorbidity, smoking history
Predictors of Progression with BCG

- 6-month (or 3 month) cystoscopic evaluation is the most significant predictor of risk of disease progression after adjustment for:
  - Stage, grade, CIS, multifocality, type of intravesical therapy.
When to abandon BCG?

<table>
<thead>
<tr>
<th>6-Mo Evaluation After BCR</th>
<th>5-Yr Progression</th>
</tr>
</thead>
<tbody>
<tr>
<td>cT1 ± pos cytology</td>
<td>100%</td>
</tr>
<tr>
<td>cTIS-Ta + pos cytology</td>
<td>100%</td>
</tr>
<tr>
<td>cTIS-Ta OR pos cytology</td>
<td>81%</td>
</tr>
<tr>
<td>Biopsy neg and neg cytology</td>
<td>26%</td>
</tr>
</tbody>
</table>

Exception: T1 @ 3 months → 100% progression
High-Risk NMIBC: Response to BCG

- Complete Response (CR) to induction BCG:
  - Papillary tumors: 55-65%
  - CIS: 50-75%

- Disease persistence @ 3 months
  - 58% CR to 2nd course of BCG
  - ~ 1/3 with tumor-free with observation alone

- Disease persistence @ 3 mos ≠ BCG refractory
Predictors of Progression: 3 month evaluation

- SWOG 8507, 593 pts with Ta or T1 TCC +/- CIS → 341 (57%) achieved clinical complete response (cCR) to induction BCG

- cCR → Survival: HR 0.6; 95% CI: 0.5-0.9; \( P = .003 \)

- Patients > 62 yrs with clinical incomplete response at 3 months have 3.1-5.1-fold higher risk of ‘disease worsening’ relative to younger pts who achieve cCR
## Cystectomy: Too Often Too Late!

<table>
<thead>
<tr>
<th>Institution</th>
<th>PT0-2</th>
<th>PT3-4</th>
<th>PN1-2</th>
</tr>
</thead>
<tbody>
<tr>
<td>MSKCC, USA</td>
<td>52%</td>
<td>48%</td>
<td>22%</td>
</tr>
<tr>
<td>USC, USA</td>
<td>51%</td>
<td>49%</td>
<td>23%</td>
</tr>
<tr>
<td>Bern SUI</td>
<td>48%</td>
<td>52%</td>
<td>24%</td>
</tr>
<tr>
<td>Leissner et al., GER</td>
<td>52%</td>
<td>48%</td>
<td>28%</td>
</tr>
<tr>
<td>Shariat et al., USA</td>
<td>57%</td>
<td>43%</td>
<td>23%</td>
</tr>
<tr>
<td>Herr et al., USA</td>
<td>55%</td>
<td>45%</td>
<td>20%</td>
</tr>
</tbody>
</table>
Early Cystectomy for NMIBC

- T1 at diagnosis
- T1 at recurrence

Post-Cystectomy Survival vs. Years from Cystectomy

Stöckle et al. Eur Urol 1987
Indications for Cystectomy on BCG

- T1 recurrence at any time
- Any CIS or Ta tumor $\geq$ 6 months after BCG
- Any recurrence on maintenance BCG
- “Worsening of disease” at 3 months

Exception: Recurrence of focal CIS or TaLG after 2+-year disease-free interval following 1 cycle of BCG
Appropriate Triggers to Abandon BCG?

- 307 pts with high-risk superficial bladder cancer treated with BCG on protocol at MSKCC 1979-84 → 90 (29%) underwent radical cystectomy (38% for superficial recurrence)

- “Early” cystectomy (< 2 yrs) for superficial recurrence assoc with 92% survival (83% overall) → DO NOT WAIT FOR INVASIVE RECURRENCE

Outcomes of Cystectomy for BCG Failures

- Cleveland Clinic: 2004-2009 → 492 RC pts → 215 (44%) underwent delayed RC after initial BCG therapy
  - Median time to RC: 20 mos (IQR: 9-48)
  - Clinical stage at RC: 141 (66%) cTIS-T1, 78 (36%) cT2

- Pathological outcomes
  - 74 (34%) → pT3-4 or pN1-2
  - 42 (20%) → pN1-2

- No difference in rate of non-organ-confined disease compared to immediate RC group (76% cT2-4)
Outcomes of Cystectomy for BCG Failures

• 5-year survival:
  – Delayed RC: 70% (95% CI: 63-77)
  – Immediate RC: 53% (95% CI: 45-61)

• No significant difference in survival (HR 0.9; 95% CI: 0.5-1.5) adjusting for age, gender, comorbidity, clinical stage at RC, time from diagnosis to RC

• 40% of deaths occurred in patients undergoing deferred RC for BCG refractory disease!

• ? BCG → making ‘curable’ patients ‘incurable’
### Appropriate Triggers to Abandon BCG?

<table>
<thead>
<tr>
<th>Comparison</th>
<th>Non-Organ-Confined Bladder Cancer</th>
<th>5-Year Overall Survival</th>
</tr>
</thead>
<tbody>
<tr>
<td>Early (&lt; 2 yrs) vs. Late (&gt; 2 yrs) RC</td>
<td>37% vs. 30%</td>
<td>45% vs. 53%</td>
</tr>
<tr>
<td>cTIS-T1 vs. cT2-4 at RC</td>
<td>30% vs. 42%</td>
<td></td>
</tr>
<tr>
<td>Early RC for cTIS-T1 vs. other</td>
<td>33% vs. 37%</td>
<td></td>
</tr>
</tbody>
</table>

*P > 0.05 for all comparisons*
BCG Failures: Role of Salvage Intravesical Therapy

• Limited role for patients unfit or unwilling to undergo radical cystectomy and diversion

• Valrubicin: 19% CR, 8% durable CR

• Gemcitabine: 50% CR, 6% durable CR

• Low-dose BCG + INF-α: 40-50% NED at 2 yrs
  – Problem: 40-50% of pts not “BCG refractory”

• CCF: Sunitinib x 2 cycles → 42% CR, 12% durable CR

Who is a candidate for salvage intravesical chemotherapy?

- Limited life expectancy, significant comorbidity
  - MSKCC → Pts > 80 yrs had similar risk of complications and cancer-specific death compared to pts < 80 yrs

- Low-grade recurrence
- Focal CIS
- Long disease-free interval after BCG

Donat et al. *J Urol* 2010
BCG: Initial Therapy for TaHG, T1, CIS

- Re-staging TUR at diagnosis in all pts
- Careful staging of the prostatic urethra
- Full-strength BCG x 6 installations is standard
- Close evaluation at 3 and 6 months
  - Cystoscopy, cytology, bladder biopsy
- Maintenance BCG if CR to BCG at 3-mo evaluation
- Limited role for salvage intravesical therapy
- Do not wait for invasive recurrence
BCG Refractory Bladder Cancer: What is the Next Step?

1. Cystectomy
2. Cystectomy
3. Cystectomy
4. Enroll in clinical trial
5. Consider TUR +/- salvage intravesical therapy or TUR for LG TCC, focal CIS, long disease-free interval after BCG in older and/or frail patient
Cleveland Clinic
Every life deserves world class care.