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, variant histology (e.g. micropapillary)
  - Prior bladder cancer history

- Patient factors:
  - Age, comorbidity, smoking history

Non-Muscle-Invasive Bladder Cancer

<table>
<thead>
<tr>
<th>Tumor Type</th>
<th>Frequency</th>
<th>Progression</th>
<th>Mortality</th>
</tr>
</thead>
<tbody>
<tr>
<td>Non-invasive</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Papilloma</td>
<td>10%</td>
<td>0-1%</td>
<td>0%</td>
</tr>
<tr>
<td>PUNLMP (G1)</td>
<td>20%</td>
<td>&lt;4%</td>
<td>&lt;1%</td>
</tr>
<tr>
<td>TaLG (G2)</td>
<td>20%</td>
<td>&lt;10%</td>
<td>&lt;5%</td>
</tr>
<tr>
<td>TaHG (G3)</td>
<td>30%</td>
<td>10-40%</td>
<td>10-25%</td>
</tr>
<tr>
<td>Invasive—T1</td>
<td>20%</td>
<td>30-50%</td>
<td>33%</td>
</tr>
<tr>
<td>Carcinoma in situ</td>
<td>18%</td>
<td>50%</td>
<td>33%</td>
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<td>10-25%</td>
</tr>
<tr>
<td>TaLG vs. T1 or HG: Different Species?</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>TaLG</td>
<td>FGFR3 mutations</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Activation Ras-MAPK pathway</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Cell proliferation</td>
<td></td>
<td></td>
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<tr>
<td></td>
<td>&quot;Non-lethal cancer&quot;</td>
<td></td>
<td></td>
</tr>
<tr>
<td>TaHG, CIS, T1</td>
<td>Loss of p53 or pRB</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Genetic instability</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>De-differentiation</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Progression</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>&quot;Potentially-lethal cancer&quot;</td>
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<td></td>
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NMIBC: 15-Year Outcomes with BCG

- 50% progression
- 34% mortality from bladder cancer
- 38% 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

Cookson et al. J Urol 1997
Bladder Cancer: Optimizing Outcomes

- “Timely” cystectomy for T1, TaHG, CIS
- Quality of radical cystectomy
- Extended pelvic lymphadenectomy
- Peri-operative systemic therapy
- Improve morbidity and HRQOL

Cystectomy: Too Often Too Late!

<table>
<thead>
<tr>
<th></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>24%</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

- Post-cystectomy survival
- Years from cystectomy

Bickle et al. Eur Urol 1987
Initial BCG is favored over immediate cystectomy in patients with high-risk, non-muscle-invasive bladder cancer (NMIBC)

- No compromise in “curability” with delayed cystectomy for BCG failures
- Improved quality of life with bladder preservation
- Avoids morbidity of radical cystectomy

Why not immediate cystectomy?

- 2-5% perioperative mortality
- 40-60% complications (10-15% major)
- ↓ QoL (urinary, bowel, sexual domains) among cystectomy patients with ileoconduit and orthotopic neobladder

Bladder cancer population:
- ~50% > 65 years
- ~50% have substantial comorbid illness

Patient selection, monitoring, and timely use of cystectomy is essential for a successful bladder preservation strategy
Patient Selection: Re-TUR

<table>
<thead>
<tr>
<th>Initial TUR Stage</th>
<th>T1</th>
<th>T2+</th>
</tr>
</thead>
<tbody>
<tr>
<td>T1IS</td>
<td>20%</td>
<td>10%</td>
</tr>
<tr>
<td>Ta</td>
<td>28%</td>
<td>5%</td>
</tr>
<tr>
<td>M. propria absent</td>
<td>17%</td>
<td>48%</td>
</tr>
<tr>
<td>M. propria present</td>
<td>29%</td>
<td>14%</td>
</tr>
</tbody>
</table>

Patient Selection: Re-TUR and Response to BCG

- 132 pts had single TUR before BCG
- 247 pts with TaHG or T1 bladder cancer
- 218 pts had re-TUR before BCG
- 76 pts (57%) had recurrent tumors at first FU cystoscopy
- 48 pts (34%) with progression
- 62 pts (38%) had recurrent tumors at first FU cystoscopy
- 16 pts (7%) with progression

Patient Selection: Improving Cystoscopy, TUR

- White-light cystoscopy: misses 25% of CIS

Porphyrin-based fluorescence cystoscopy using blue and white light with intravesical hexaminovulinate (HAL, Cysview, Hexvix)
Patient Selection: Improving Cystoscopy, TUR

- Detection of CIS and papillary UC in 15-30% and 20-25% of pts, respectively

- 501 pts Ta or T1 randomized to TUR +/- intravesical hexaminovulinate and blue-light cystoscopy
- Intravesical therapy: 20% BCG, 25% chemoh
- Median FU: 55 mos
- Median time to recurrence:
  - 16.4 vs. 9.6 months (P = 0.04)
- cT2-4 cancer:
  - 3.3% vs. 5.7% (P = 0.09)
- Cystectomy:
  - 4.0% vs. 7.9% (P = 0.19)

Patient Selection: Improving Cystoscopy, TUR

Maintenance BCG: the Standard

- SWOG 8507: Maintenance BCG vs. observation in patients achieving CR to induction BCG

<table>
<thead>
<tr>
<th>Maintenance</th>
<th>Standard</th>
</tr>
</thead>
<tbody>
<tr>
<td>Recurrence</td>
<td>60%</td>
</tr>
<tr>
<td>Progression</td>
<td>76%</td>
</tr>
<tr>
<td>Survival</td>
<td>83%</td>
</tr>
</tbody>
</table>

- Only 10% in maintenance arm received prescribed dose
When to abandon BCG?

6-Mo Evaluation After BCG 5-Yr Progression

cT1 ± pos cytology 100%
cTIS-Ta + pos cytology 100%
cTIS-Ta OR pos cytology 81%
Biopsy neg and neg cytology 26%

Exception: T1 @ 3 months → 100% progression

Predictors of Post-Cystectomy Survival
Analysis of SWOG 8710

<table>
<thead>
<tr>
<th>Parameter</th>
<th>HR (95% CI)</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>No neoadjuvant chemotherapy</td>
<td>1.01 (0.7, 1.4)</td>
<td>.3</td>
</tr>
<tr>
<td>Age &gt; 65 yrs</td>
<td>1.5 (1.04, 3.6)</td>
<td>.031</td>
</tr>
<tr>
<td>Pathologic stage 3-4</td>
<td>2.3 (1.5, 3.6)</td>
<td>.0002</td>
</tr>
<tr>
<td>Positive nodes</td>
<td>1.8 (1.02, 2.5)</td>
<td>.042</td>
</tr>
<tr>
<td>Positive margins</td>
<td>2.7 (1.5, 4.9)</td>
<td>&lt;.0001</td>
</tr>
<tr>
<td>&lt; 10 nodes removed</td>
<td>2.0 (1.4, 2.8)</td>
<td>&lt;.0001</td>
</tr>
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Quality of surgery matters!
Quality of Cystectomy: SWOG 8710

- 317 patients, 1987-1998, 106 surgeons
  - 36% fellowship-trained urologic oncologist
  - 82% of surgeons performed < 5 RC
- PLND:
  - Standard (54%), limited (37%), none (9%)
  - 50% cases < 10 nodes removed
- Positive surgical margins: 10%
  - 4% urologic oncologist, 16% other
- Local recurrence:
  - 5% urologic oncologist, 25% other

Type of surgeon was a significant predictor of survival, local recurrence, number of nodes removed

Pelvic Lymphadenectomy: Importance

- 20-30% RC pts have lymph node metastasis
- 25-35% node-positive patients cured by RC
- Prognosis related to:
  - Primary tumor stage
  - Extranodal extension
  - Number of positive lymph nodes
  - Number of lymph nodes removed

Can standards for PLND be established?

- RC cures 20-35% of patients with positive nodes
  - T nodes removed → T survival
  - Dose-response curve: no limit

Koppie et al. CANCER 2007
Pelvic Lymphadenectomy: Importance

- 20-30% RC pts have lymph node metastasis
- 25-35% node-positive patients cured by RC

Prognosis related to:
1. Primary tumor stage
2. Extrarectal extension
3. Number of positive lymph nodes
4. Number of lymph nodes removed

#3 and #4 related to the completeness and extent of PLND

Can standards for PLND be established?

Standard PLND

Extended PLND
Mapping Studies for Nodal Metastases
Extended PLND

Distribution of Nodal Metastasis by Zone

Common iliac and presacral involvement as common as distal nodes.
Can standards for PLND be established?

- Level I: 21%
- Level II: 19%
- Level III: 7%

28% PN+

Can standards for PLND be established?

**Extended PLND: Therapeutic Potential**

- 19% pN+
- 6% pN+ pts had skip metastasis to level II-III (1.2% overall)
- Survival of pts with level II-III involvement (37%) was similar to overall pN+ (39%) and level I involvement only (42%)
- Survival not related to no. LN removed -- argues extended template more important than adequacy of distal dissection

336 pts, all extended PLND, median FU 3.6 yrs, Steven et al. J Urol 2007

**Urinary Diversion: Options**

- Cutaneous
  - Diversion to skin (stoma)
  - Incontinent, e.g. ileostomy
  - Continent, e.g. Indiana pouch

- Orthotopic
  - Diversion to urethra
  - Neobladder, Void per urethra, e.g. Studer
Issues Affecting Urinary Diversion Selection

Cancer Control
  Risk of LCR
  Prior radiation
  Urethral or bladder neck involvement
  Need for adjuvant therapy
General Health
  Age
  Prior surgery
  Hepatic and renal function
  Comorbidity
  Body habitus
Technical
  Urethra status
  Tumor site
  Ability to catheterize
  Mesentery length
  OR time
Quality of Life
  Body image
  Sexual function
  Compliance
  Daily maintenance

Contraindications to Continent Diversion

**ABSOLUTE**
- Impaired renal function
- Impaired hepatic function
- Physical or mental impairment (re: self-cath)
- Unmotivated patient
- Positive urethral margin or BN involvement (female)

**RELATIVE**
- Advanced age
- Comorbidity
- Prior radiation
- Bowel disease
- Urethral pathology
- High-risk of LCR (gross LN+, SM+, sarcoma)

Cleveland Clinic
Orthotopic Neobladder

**ADVANTAGES**
- Recapitulates normal anatomy
- High daytime continence rate
- Low technical complications
- Low urethral recurrence rate
- High patient satisfaction
- Long-term safety re: renal function

**DISADVANTAGES**
- Need for timed voiding
- Men:
  - Nighttime incontinence
  - 10% retention → self-cath
- Women:
  - 1/3 dry, 1/3 wet, 1/3 retention
  - ? Higher risk of local recurrence
- Longer OR time (60 min)
- Metabolic complications
- Poor renal fan
- Delivery of chemotherapy

Indiana Pouch
Continent Cutaneous Diversion
**Continent Cutaneous Diversion**

**ADVANTAGES**
- Avoids external appliance
- Excellent continence rates
- High patient satisfaction
- Long-term safety for renal function

**DISADVANTAGES**
- Timed self-catheterization
- 10-20% incontinence
- Highest technical problems
  - Stomal stenosis
  - Incontinence: inadequate valve
- Longer OR time (60 min)
  - Most technically complex
- Higher metabolic complications
- GI problems: diarrhea, B12
- Poor renal function
- Delivery of chemotherapy

---

**Ileocecal Cutaneous Diversion**

**Incontinent Cutaneous Diversion**

**ADVANTAGES**
- Simplest to perform
- Quickest to perform
- Lowest risk of complications
- Avoids issues re: motivation and physical or mental impairments

**DISADVANTAGES**
- Body image
- Requires appliance (drainage bag)
- Appliance problems (poor fit, leak, etc) and cost

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