Optimizing Selection Criteria and Response to Bladder Preserving Chemoradiation for Invasive Urothelial Cancer

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09/12/2015
Disclosure

No conflict of Interest
Learning Objectives

1. Understand appropriate patient-selection for bladder-sparing therapy vs. cystectomy for bladder cancer

2. Understand the evidence for the efficacy and toxicity of bladder-sparing therapy

3. Understand the radiation and chemotherapy regimens for bladder-sparing therapy
Background

- 70,000 each year in United States
  - 52,000 men, 18,000 women
- 30% muscle-invasive
- 14,680 deaths
- Median age 65

Jemal A, CA Cancer J Clin 2010
T-Staging of Bladder Cancer

1 Epithelium
2 Subepithelial connective tissue
3 Muscle
4 Perivesical fat

T1: Tumor invades local organs
T4b: Tumor invades pelvic or abdominal walls
T-Staging of Bladder Cancer

- Ta, cis, T1: based upon TURBT
- T2-4a: for surgeons - *pathologic* diagnosis
- For organ conservers - *clinical* diagnosis  
  (Based on TURBT only and *under staging is common*)
- T4b: usually clinical diagnosis
Establish depth of bladder invasion and local extent:

- **TURBT** down to & including muscularis proprium (biopsy alone is insufficient)

- Prostatic urethral biopsies

- **CT or MRI A/P - Hydronephrosis and nodes**
  
  *(Understaging is common)*

**DM:**

- Bone scan and chest CT
What are the indications for resection after initial TURBT?

Repeat resection should be performed if:

1. Incomplete resection of gross tumor

2. High-grade disease and no muscle in specimen

3. Any T1 lesion
   • Up to 40% residual tumor on 2nd resection
Which pts can be observed after maximum TURBT?

- 1. Completely resected
- 2. Ta
- 3. Grade 1 (no high grade)
- 4. No residual abnormality on urine cytology
Treatment Options for Muscle Invasive Transitional Cell Carcinoma
**Primary Treatment**

- **Radical cystectomy**\(^b\) and strongly consider neoadjuvant cisplatin-based combination chemotherapy (category 1)
  - or
- Segmental (partial) cystectomy\(^b\) (highly selected patients with solitary lesion in a suitable location; no Tis) and consider neoadjuvant cisplatin-based combination chemotherapy\(^m\)
  - or
- Bladder preservation\(^b\) following maximal TURBT with concurrent chemotherapy\(^m\) + RT\(^n\) (category 2B)\(^o\)
  - or
- For patients with extensive comorbid disease or poor performance status: TURBT alone\(^b\) or RT + chemotherapy\(^m, n\) or Chemotherapy alone\(^m\)

**Adjuvant Treatment**

- Consider adjuvant chemotherapy\(^m\) (category 2B) based on pathologic risk (pT3-4 or positive nodes) if no neoadjuvant treatment given
  - or
- Consider adjuvant RT\(^n\) (category 2B) or chemotherapy\(^m\) (category 2B) based on pathologic risk (pT3-4, positive nodes, positive margin, or high-grade) if no neoadjuvant treatment given

**Clinical Staging**

- **Negative nodes**
  - Abdominal/pelvic CT or MRI
    - cT2
    - or
    - for T4b with positive nodes

- **Positive nodes**
  - See BL-6 (follow treatment as for T4b with positive nodes)

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\(^b\) See Principles of Surgical Management (BL-A).
Radical Cystectomy

- **Men**: Prostate, seminal vesicles
- **Females**: Uterus, cervix, ovaries, anterior vagina
- **Both**: Urinary bladder, distal ureters, pelvic peritoneum
- **Urinary Diversion**:
  - Conduit via abdominal wall
  - *Orthotopic neobladder*
- **Bilateral pelvic nodal dissection (>10LN) the more the better (Koppie et al Cancer 2006)**
Radical Cystectomy

- Radical cystectomy w/ PLND is currently SOC for MIBC
- 5-year OS rates ranges 55% to 60%

### Table 2  Select Prospective Clinical Trials and Large Institutional Series of Radical Cystectomy for Muscle-Invasive Bladder Cancer

<table>
<thead>
<tr>
<th></th>
<th>N</th>
<th>Clinical Stage</th>
<th>Median Age (y)</th>
<th>Induction Chemotherapy</th>
<th>5-Year Overall Survival (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Phase III Trials</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Nordic(^{25})</td>
<td>317</td>
<td>cT2–4a,Nx</td>
<td>66–67</td>
<td>None vs CM × 3</td>
<td>46 vs 53</td>
</tr>
<tr>
<td>US Intergroup(^{21})</td>
<td>317</td>
<td>cT2–4a,N0</td>
<td>63</td>
<td>None vs MVAC</td>
<td>43 vs 57</td>
</tr>
<tr>
<td><strong>Large institutional Series</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>USC/Bern(^{22})</td>
<td>959</td>
<td>pT2–3c,N0</td>
<td>67</td>
<td></td>
<td>≈50</td>
</tr>
</tbody>
</table>
Bladder Preservation

- For pts w/ MIBC who are non-cystectomy candidates, **trimodality bladder preservation therapy offers a curative treatment regimen** that is well tolerated in elderly patients, and therefore should be considered for ALL patients.

- For pts eligible for radical cystectomy but motivated to preserve bladders, **careful patient selection based on pretreatment characteristics** is important to maximize the probability of success.
Bladder Preservation

Maximal safe TURBT

Radiation and concurrent chemotherapy

Cystoscopic assessment of treatment response

Incomplete response

Radical cystectomy ± adjuvant chemotherapy

Complete response

Complete chemoradiation ± adjuvant chemotherapy

Recurrent invasive tumor

Long-term cystoscopic surveillance
## How does bladder preservation compare to surgery?

### Contemporary Group Trials in Invasive Bladder Cancer—
all in clinically staged patients (cT2-4a)

<table>
<thead>
<tr>
<th>Group</th>
<th>Treatment</th>
<th>Number</th>
<th>5 yr OS</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Surgery</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>SWOG</td>
<td>Cystectomy + NCT</td>
<td>317</td>
<td>47%</td>
</tr>
<tr>
<td>Italian</td>
<td>Cystectomy + NCT</td>
<td>206</td>
<td>54%</td>
</tr>
<tr>
<td><strong>Bladder Preservation</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>RTOG</td>
<td>TURBT+XRT</td>
<td>123</td>
<td>49%</td>
</tr>
<tr>
<td></td>
<td>Cisplatin + NCT</td>
<td></td>
<td></td>
</tr>
<tr>
<td>SWOG</td>
<td>TURBT+XRT Cis/5-FU</td>
<td>25</td>
<td>45%</td>
</tr>
<tr>
<td>MGH</td>
<td>TURBT+XRT + chemo</td>
<td>348</td>
<td>52%</td>
</tr>
</tbody>
</table>
Key Points for Modern Bladder Preserving Approaches

1. Patient Selection
2. Importance for Life-Long Bladder Surveillance
3. QOL after Bladder Preservation
1. Patient Selection

- Solitary T2 or early T3 tumors < 6 cm

- No tumor-associated hydronephrosis
  - RTOG 8903, pts w/ hydronephrosis, vs. not, had worse CR rates (38% vs 64%; P=.02) and 5-yr OS (33% vs 54%; P=.06).

- Tumors allowing a visibly complete/Maximal safe TURBT

- Invasive tumors not associated with extensive carcinoma in situ

- Adequate renal function to allow cisplatin concurrent with radiation
  - Alternative chemotherapy regimens now exist
Consideration of Age

- SEER: 12,722 patients, 1988-2006
- Cystectomy for M0 bladder cancer
- Peri-operative mortality (90 days)
  - <70 years: 2%
  - 70-79 years: 5.4% (MVA OR: 2.8)
  - ≥ 80 years: 9.2% (MVA OR: 5.0)

Liberman D, Urol 77:660-668, 2011
### Ideal bladder preservation candidate

<table>
<thead>
<tr>
<th>Contraindications to Radical Cystectomy</th>
<th>Contraindications to Trimodality Therapy</th>
</tr>
</thead>
<tbody>
<tr>
<td>Significant comorbidities increasing operative mortality</td>
<td>Patients at highest risk for local failure (e.g., hydronephrosis, clinical T3b–4 disease)</td>
</tr>
<tr>
<td>Age &gt;75–80 years even without significant comorbidities</td>
<td>Maximal TURBT cannot be performed safely (e.g., large tumor, tumor in diverticulum or at the bladder dome)</td>
</tr>
<tr>
<td>Avoidance of an immediate cystectomy is a strong patient preference</td>
<td>Poor candidate for radiosensitizing chemotherapy</td>
</tr>
<tr>
<td>Patient unable to manage a urinary diversion (e.g., ileostomy) that may be necessary</td>
<td>Presence of extensive carcinoma in situ</td>
</tr>
<tr>
<td></td>
<td>Poor candidate for radiation therapy (e.g., prior pelvic radiation, inflammatory bowel disease, poor baseline bowel or bladder function)</td>
</tr>
<tr>
<td></td>
<td>Histologies other than urothelial carcinoma</td>
</tr>
</tbody>
</table>
Outcomes of bladder preservation in RTOG studies

- Pooled Analysis of Radiation Therapy Oncology Group Protocols 8802, 8903, 9506, 9706, 9906, and 0233
- Median age of patients was 66 years
  - T2 61%, T3 35%, T4a 4%
- CR rate w/ CMT 69%
- 5 year OS rates 57%
- 10 year OS 36%
- In patients who ultimately required salvage cystectomy for nonresponse to CMT or recurrent disease still had a 5-year DSS of 60% and 10-year DSS of 47%

Mak RH, JCO 32:3801-3809, 2014
Outcomes of bladder preservation in RTOG studies

Mak RH, JCO 32:3801-3809, 2014
2. Life-Long Bladder Surveillance

- 1/3 of pts require cystectomy for tumor persistence or invasive recurrence
- 5 and 10 year disease specific survival rates following prompt salvage cystectomy are 48% and 40% (60% and 47% in pooled RTOG series)
3. QOL after Bladder Preservation

- MGH experience
- Urodynamics: “normal” in 75% of surviving patients
- QOL: All comers
  - **Urinary:** urgency (15%)
  - flow difficulty (6%)
  - **lacking control** (19%)
  - **GI:** diarrhea (8%)
  - cramping (13%)
  - mucus (4%)
  - tenesmus (2%)
  - **difficult control** (22%)
  - Erectile function intact: 54%
  - High overall QOL SF-36
Seven percent of patients experienced a late grade 3 pelvic toxicity
- 5.7% GU and 1.9% GI.

Only one of nine patients did a grade 3 GU toxicity persist

Notably, no late grade 4 toxicities and no treatment-related deaths.
Chemotherapy regimens for concurrent treatment

- Active radiosensitizing drugs include:
  - Cisplatin,
  - Paclitaxel,
  - 5-FU,
  - Mitomycin C,
  - Gemcitabine and tumor hypoxia-reducing drugs

- Can’t substitute Carbo for Cis
RT Technique for Bladder Cancer

Nodal disease is present in 20-40% at diagnosis

- Common iliac nodes: 19%
- External iliac nodes: 65%
- Internal iliac nodes: 15%
- Perivesical LN 75%

Bladder Cancer - Lymphatic Pathway of Spread
Small Pelvic Fields by 3-D

Nodal XRT fields (40 to 45Gy) are designed to conserve small bowel for urinary diversions should they be needed.
Tumor Boost Fields by 3-D

- Only partial bladder is given the high XRT dose (total 65 Gy)
- Incorporate all TURBT and radiographic information
- Simulate and treat with an empty bladder
- 2-4 beams
# IMRT Doses

<table>
<thead>
<tr>
<th>Target volumes</th>
<th>Structures</th>
<th>Total dose and fractionations</th>
</tr>
</thead>
<tbody>
<tr>
<td>Small pelvic fields (include PTV₁)</td>
<td>Internal and external iliac vessels plus 7-mm margin</td>
<td>51 Gy/30 fractions at 1.7 Gy/Fx</td>
</tr>
<tr>
<td>Whole bladder field (PTV₂)</td>
<td>Include the entire bladder and prostate plus 1 cm</td>
<td>54 Gy/30 fractions at 1.8 Gy/Fx</td>
</tr>
<tr>
<td>Tumor boost field (CTV₃)</td>
<td>Area of bladder involved by tumor based on TURBT or palpable disease plus 7 mm</td>
<td>64.5 Gy/30 fractions at 2.15 Gy/Fx</td>
</tr>
</tbody>
</table>
PTV 2
Bladder tumour +1.5cm
64Gy/32fractions or
55Gy/20f
+/- 5%

'Non tumour' Bladder
52Gy /32f

PTV 1
Non tumour bladder + 1.5cm
80% of PTV2 dose (Minimum
75%)
Future Directions

- 3 cohorts (2 surgery, 1 RT)
- TIP 60 predictive, p16 prognostic, MRE11 predictive
- ATM, Rb, Ki67, p53 not associated with DSS
- Cystectomy better 5 yr DSS 72 vs 38%, p=0.01
  - Low MRE11 and High TIP60
- Radiotherapy better 5 yr DSS 78 vs 40%, p=0.01
  - High MRE11 and low TIP60
- P16 positive patients improved DSS in both groups
Cystectomy Candidates

- T3-T4a w/ hydronephrosis: Cystectomy.
- T4a w/ prostate stromal invasion: Cystectomy.
- T2-T3: TURBT + CRT (QD or BID RT) w/ prompt cystectomy for failure
- Biopsy positive LN: Systemic chemo, then individualized local therapy

Non-Cystectomy Candidates

- TURBT
- Radiation to 60 – 64 Gy
- Daily radiation more tolerable
- If patient unable to tolerate cisplatin: (concurrent)
  - 5FU, Mitomycin C (BC2001, Level 1)
  - Gemcitabine may be alternative
- Node +: chemo, individualize local therapy (likely distant failure)
Conclusions

- Modern CMT for bladder sparing results in good long-term bladder function (~80% of survivors).

- The acceptance of CRT should not be limited by concerns of high rates of late pelvic toxicity.

- Impact of selective bladder sparing therapy to pts QoL represents a unique opportunity for urologic surgeons, radiation oncologists, and medical oncologists to work hand in hand in a truly multidisciplinary manner.

- The cure rates from CMT is comparable to cystectomy- NOT a default treatment for only unfit patients.

- Need for clinical trials to validate predictive biomarkers. This will provide better rationale for all GU specialists to offer organ-sparing treatment to a significant subset of MIBC pts – not just those over 75.
References

Long-Term Outcomes in Patients with Muscle-Invasive Bladder Cancer after Selective Bladder-Preserving Combined-Modality Therapy: A Pooled Analysis of Radiation Therapy Oncology Group Protocols 8802, 8903, 9506, 9706, 9906, and 0233; Mak RH, JCO 32:3801-3809, 2014


THANK YOU