“Radical cystectomy is the only effective treatment choice for patients with operable invasive bladder cancer”

Peter Black
Department of Urologic Sciences
Grand Rounds – Oct 13, 2010

“Operable invasive bladder cancer”

- cT2-T4a (“MIBC”)
- cN0
- same issues likely apply to BCG refractory high-grade T1
- implies curative intent
Optimal treatment for MIBC

1. Eradication of tumor in bladder.
2. Preserve normal urinary function.
3. Preserve normal sexual function.
4. Minimal other adverse effects.
5. Long-term survival.

NCCN Guidelines

- Radical cystectomy, consider neoadjuvant chemotherapy
- Segmental cystectomy (solitary lesion, no Cis)
- Selective bladder sparing (maximal TURBT + chemo + XRT)
  - If extensive comorbidities: TURBT alone, XRT alone, chemo alone
  - Consider adjuvant chemotherapy for T3 and/or N+
  - Salvage cystectomy for recurrent/persistent disease ≥T1
EUA Guidelines

- Cystectomy is the preferred curative treatment for localised bladder cancer (3)
- A higher case load reduces morbidity and mortality of cystectomy (3)
- Radical cystectomy includes removal of regional lymph nodes, the anatomical extent of which has not been sufficiently defined (3)
- Radical cystectomy in both sexes must not include the removal of the entire urethra in all cases, which may then serve as outlet for an orthotopic bladder substitution (3)
- Terminal ileum and colon are the intestinal segments of choice for urinary diversion (3)
- The type of urinary diversion does not affect oncological outcome (3)

Radical Cystectomy - Outcomes

- Single institutions
  - USC
  - Bern
  - Ulm
- Clinical trials
- Multicentre
  - Bladder Cancer Research Consortium
  - Canadian Bladder Cancer Network
Bladder Cancer Research Consortium

- combined retro- and prospective
- 1994 - 2003
- 888 patients
- 3 centres: Baylor College (Houston), Johns Hopkins (Baltimore), UT Southwestern (Dallas)

Shariat, J Urol, 176:2414-2422, 2006
Editorial comment

• “These data provide a benchmark for comparison of future reports of outcomes with multimodality treatment and bladder sparing regimens.”

M. Cookson
Canadian Bladder Cancer Network

- 2287 patients from 8 centres
- 1998 – 2008
- 5 year OS 57%
  CSS 67%
- local recurrence: 6%

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Survival probability

Cancer specific survival

Time (Year)

n=863
n=633
n=507
```

P<0.0001
1054 Cystectomies at USC

Stein JCO 2001

788 Cystectomies in Ulm
507 Cystectomies at Bern

Recurrence free survival
(73% at 5 years)

Overall survival
(62% at 5 years)
Local Control vs. Overall Survival

- Cystectomy provides 80-90% local control at 5 years, but only ~60% cancer specific survival.
- Presumably due to micrometastasis:
  - Bladder cancer as systemic disease
  - Can XRT or surgery make a difference?

Recurrence in USC series

- Recurrence in 311 of 1054 (30%)
  - Distant recurrence in 234 (75%)
  - Isolated local recurrence in 77 (25%)
- Median time to any tumor recurrence was 12 months.
- 86% of recurrences occurred within 3 years.

Stein JCO 2001
Recurrence in Bern Series

- recurrence in 219 of 507 (43%)
  - distant metastases in 179 (82%)
  - isolated local recurrence in 40 (18%)
- median time to recurrence 16 months
- 93% of recurrences occurred within 3 years


Optimizing Outcome from Cystectomy

- these series are “all comers”
- each series with different case mix
- need to consider optimized delivery of care:
  - neoadjuvant chemo (randomized trials)
  - extended PLND
**SWOG – 8710 – Neoadjuvant Chemo**

**Overall survival**

- M-VAC and cystectomy (98 deaths; median survival, 77 mo)
- Cystectomy alone (108 deaths; median survival, 46 mo)

<table>
<thead>
<tr>
<th>Months after Randomization</th>
<th>Survival (%)</th>
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<tbody>
<tr>
<td>0</td>
<td>100</td>
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<tr>
<td>12</td>
<td>57%</td>
</tr>
<tr>
<td>24</td>
<td>43%</td>
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<table>
<thead>
<tr>
<th>No. at Risk</th>
<th>M-VAC and Cystectomy</th>
<th>Cystectomy alone</th>
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<tbody>
<tr>
<td>153</td>
<td>112</td>
<td>92</td>
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<tr>
<td>154</td>
<td>88</td>
<td>67</td>
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<td>92</td>
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<td>46</td>
<td>23</td>
<td>18</td>
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<tr>
<td>23</td>
<td>6</td>
<td>7</td>
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</table>

**Table 1: Baseline Characteristics of Patients**

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<thead>
<tr>
<th></th>
<th>Initial Surgery</th>
<th>Initial Chemotherapy</th>
<th>All Patients</th>
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<tbody>
<tr>
<td>No. of patients</td>
<td>70</td>
<td>70</td>
<td>140</td>
</tr>
<tr>
<td>Age, years</td>
<td></td>
<td></td>
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</tr>
<tr>
<td>Median</td>
<td>67</td>
<td>66</td>
<td>66</td>
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<tr>
<td>Range</td>
<td>32.79</td>
<td>36.79</td>
<td>32.79</td>
</tr>
<tr>
<td>Sex</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Male</td>
<td>45</td>
<td>55</td>
<td>100</td>
</tr>
<tr>
<td>Female</td>
<td>25</td>
<td>15</td>
<td>40</td>
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<tr>
<td>Clinical stage</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>T1a</td>
<td>23</td>
<td>21</td>
<td>44</td>
</tr>
<tr>
<td>T1b</td>
<td>39</td>
<td>42</td>
<td>81</td>
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<tr>
<td>T1c</td>
<td>6</td>
<td>7</td>
<td>13</td>
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<tr>
<td>Upper tract</td>
<td>2</td>
<td>0</td>
<td>2</td>
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<tr>
<td>Histology</td>
<td></td>
<td></td>
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</tr>
<tr>
<td>TCC, NOS</td>
<td>44</td>
<td>42</td>
<td>86</td>
</tr>
<tr>
<td>TCC + other</td>
<td>19</td>
<td>20</td>
<td>39</td>
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<tr>
<td>Non-TCC</td>
<td>7</td>
<td>8</td>
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<tr>
<td>Non-TCC, element</td>
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<td></td>
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<tr>
<td>Squamous</td>
<td>11</td>
<td>12</td>
<td>23</td>
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<td>Adenocarcinoma</td>
<td>7</td>
<td>13</td>
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<tr>
<td>Sarcomatoid</td>
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<td>6</td>
<td>11</td>
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<td>Microspapillary</td>
<td>1</td>
<td>3</td>
<td>4</td>
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<tr>
<td>Small cell</td>
<td>1</td>
<td>2</td>
<td>3</td>
</tr>
<tr>
<td>Other</td>
<td>3</td>
<td>2</td>
<td>5</td>
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<tr>
<td>Registration &gt; 6 months from diagnosis</td>
<td>18</td>
<td>17</td>
<td>35</td>
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<tr>
<td>Hydronephrosis</td>
<td>30</td>
<td>26</td>
<td>56</td>
</tr>
</tbody>
</table>

**Abbreviation: NOS, not otherwise specified.**

*All patients had lymphovascular invasion on TURBx.*

†Many patients had more than one non-TCC pattern.
SWOG 8710 – Role of PLND

Overall survival

Recurrence free survival

PLND: Bern vs. Cleveland

Limited PLND at CC (n=336) vs. extended PLND in Bern (n=322)
SWOG Randomized Trial - PLND

- projected to start in Jan 2011
- ~ 650 patients
- multicentre US/Canada
- T2-T4a, N0
- randomized to extended vs. standard PLND (photographic QC)

Bladder Cancer Quality Care Initiative

- “Bladder Cancer Think Tank”
- multicentre Canada/US
- all patients with T2-T4a, N0 bladder cancer to get:
  1. med-onc consult pre-op
  2. extended PLND
- if not, why not?
Who is undergoing cystectomy?

- SEER 1992-2003
- all patients with bladder cancer
- 26,140 cystectomy
- 25,895 radiation therapy

Who is undergoing cystectomy?

- SEER/Medicare analysis of all patients >66 years with “stage II” bladder cancer 1992 to 2002
- 3262 patients

Gore, JNCI, Vol. 102, June 2, 2010
<table>
<thead>
<tr>
<th></th>
<th>Cystectomy</th>
<th>XRT/chemo</th>
<th>Surveillance</th>
</tr>
</thead>
<tbody>
<tr>
<td>Total</td>
<td>678 (21%)</td>
<td>922 (28%)</td>
<td>1662 (51%)</td>
</tr>
<tr>
<td>Age mean</td>
<td>75 yr</td>
<td>79 yr</td>
<td>81 yr</td>
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<tr>
<td>Age</td>
<td>&lt;70</td>
<td>20%</td>
<td>10%</td>
</tr>
<tr>
<td></td>
<td>70-74</td>
<td>34%</td>
<td>16%</td>
</tr>
<tr>
<td></td>
<td>75-79</td>
<td>28%</td>
<td>28%</td>
</tr>
<tr>
<td></td>
<td>≥80</td>
<td>18%</td>
<td>46%</td>
</tr>
<tr>
<td>Charlson</td>
<td>0</td>
<td>78%</td>
<td>62%</td>
</tr>
<tr>
<td></td>
<td>1</td>
<td>15%</td>
<td>24%</td>
</tr>
<tr>
<td></td>
<td>2</td>
<td>5%</td>
<td>9%</td>
</tr>
<tr>
<td></td>
<td>≥3</td>
<td>2%</td>
<td>5%</td>
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</table>

Gore, JNCI, Vol. 102, June 2, 2010
What about the elderly (>80yr)?

- USC: increased risk of early but not late complications; no difference in post-operative mortality
- multiple other series confirm safety and efficacy of radical cystectomy in octogenarians

If old patient with comorbidities...

- single modality with best efficacy is without doubt surgery
- radiation alone inferior
- sending these patients for XRT may be a mistake, unless able to receive optimal trimodal care
Why not radiotherapy?

- Survival data?
- Late toxicity?
- Late recurrence?
- Future neobladder?
- Second malignancies?
- Not “because the patient really wants to keep his bladder”

<table>
<thead>
<tr>
<th>YR</th>
<th>N</th>
<th>RFS</th>
<th>DSS</th>
<th>OS</th>
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<tr>
<td>Austria</td>
<td>2010</td>
<td>75</td>
<td>3yr – 40</td>
<td>3yr – 56</td>
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<tr>
<td>Egypt</td>
<td>2010</td>
<td>33</td>
<td>1yr - 39</td>
<td>1yr - 64</td>
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<tr>
<td>Erlangen</td>
<td>2009</td>
<td>525</td>
<td></td>
<td>5yr - 56</td>
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<tr>
<td>Italy</td>
<td>2006</td>
<td>459</td>
<td>3yr - 33</td>
<td>3yr - 56</td>
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<tr>
<td>Denmark</td>
<td>2004</td>
<td>292</td>
<td></td>
<td>3yr - 31 5yr – 21</td>
</tr>
<tr>
<td>France</td>
<td>2004</td>
<td>60</td>
<td>5yr – 42</td>
<td>5yr - 54</td>
</tr>
<tr>
<td>RTOG99-06</td>
<td>2009</td>
<td>80</td>
<td>5yr - 56</td>
<td>5yr - 71</td>
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<tr>
<td>RTOG97-06</td>
<td>2003</td>
<td>47</td>
<td>3yr – 58*</td>
<td>3yr – 61</td>
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<tr>
<td>RTOG95-06</td>
<td>2000</td>
<td>30</td>
<td>3yr – 32*</td>
<td>3yr – 83</td>
</tr>
<tr>
<td>RTOG89-03</td>
<td>1998</td>
<td>99</td>
<td></td>
<td>3yr – 59</td>
</tr>
</tbody>
</table>
Cochrane Review 2001

• three randomized trials
• pre-op XRT (approx 40 Gy) + cystectomy, versus definitive XRT (approx 60-70 Gy) + salvage cystectomy
• clear superiority of surgery
Late Recurrences?

- most studies have very short follow-up
- those with longer f/u (eg. Erlangen) do not show rising recurrence rates later
  - increased risk of progression and need for cystectomy for NMIBC
- maybe irrelevant in older patients

Second Cancers after Radiation

- increased rates of secondary bladder malignancies after external beam radiation therapy for:
  - gynaecological malignancies (RR 2-4)
  - prostate cancer (1.42 in SEER analysis; 1.88 in Nieder, J Urol 2008)
- rectal ca RR 1.26 after EBRT for CaP
- soft tissue malignancies?
Late Toxicity?

- 4 randomized trials
- 157 patients who received multimodal therapy and were alive with bladder intact 2 years later
- mean f/u 5.4 yrs
- grade 3 GU tox in 6% and GI in 2%

Future neobladder?

• salvage cystectomy after radiation therapy is usually followed by ileal loop diversion or continent cutaneous reservoir
• neobladder not impossible, but appears to be accompanied by higher risk of complications

If patient is to undergo XRT….

• avoid:
  – Cis
  – multifocal disease
  – hydronephrosis
  – large tumours (>5cm)
• ensure:
  – adequate bladder capacity
If patient is to undergo XRT….

- multimodal!
- maximal TURBT; r/o Cis
- concomitant chemotherapy
- close urologic surveillance
- salvage cystectomy if needed

Multidisciplinary Bladder Cancer Clinic

- Med Onc: every patient evaluated for peri-operative chemotherapy
- Rad Onc: XRT discussed (but not encouraged); adjuvant/neoadjuvant?
- Surgery: better outcomes after cystectomy at high volume centre
- Clinical Research: enrol patients on trials