Bladder Preservation: Modern Approaches and Outcomes

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Duke Cancer Institute
Disclosures

• Research Funding: Janssen Pharmaceuticals

• Advisory Board: BlueEarth Diagnostics

• Committee Member: ASTRO, NRG, SMSNA
Outline

• History of Bladder Conservation

• Myths and Fears

• Who should be Considered

• How It Works
History of Radiation for Bladder Cancer

- 1960s: cystectomy alone “disappointing”
- 1960s/1970s: definitive RT not effective
- 1970s: PRE-OP RT (Whittmore MSKCC) “gratifyingly improved”
  - RCTs showed no benefit

Cummings Semin Oncol 1979; 6:220.
**Role of Radiation: Pre-op**

<table>
<thead>
<tr>
<th>Randomized Trials</th>
<th>N</th>
<th>Stage</th>
<th>Dose (Gy)</th>
<th>5y OS (%) + v - RT</th>
</tr>
</thead>
<tbody>
<tr>
<td>Bloom 1982</td>
<td>189</td>
<td>T3</td>
<td>40</td>
<td>38 v 29, NS</td>
</tr>
<tr>
<td>Anderstrom 1983</td>
<td>44</td>
<td>T1-T3</td>
<td>32-54</td>
<td>75 v 61, NS</td>
</tr>
<tr>
<td>Smith 1997</td>
<td>140</td>
<td>Tis-T3</td>
<td>20</td>
<td>43 v 53, NS</td>
</tr>
</tbody>
</table>

**Conclusion:** no advantage to pre-operative RT
History of Radiation for Bladder Cancer

- 1960s: cystectomy alone “disappointing”
- 1960s/1970s: definitive RT not effective
- 1970s: PRE-OP RT (Whittmore MSKCC) “gratifyingly improved”
  - RCT showed no benefit
- 1980s: chemotherapy reduced systemic failures
- 1980s: MGH subset analysis showed improvement in papillary tumors, complete resection

Cummings Semin Oncol 1979; 6:220.
National Bladder Cancer Collaborative Group

• 1980 – phase II RT + cisplatin definitive tx
  – unresectable T2-4
  – 70 mg/m² q3 wks x 8 cycles initiating 4 wks after TURBT
  – 64.8 Gy four-field box
  – Cysto 4 weeks post RT

Treatment of Invasive Bladder Cancer by Cisplatin and Radiation in Patients Unsuited for Surgery

Shipley JAMA 1987; 258:931.
National Bladder Cancer Collaborative Group

- Complete Response by Cysto: 77%
- Of those with CR, 73% remained disease free

Shipley JAMA 1987; 258:931.
# Bladder Preservation Trials 1988-2007

## Summary of major bladder organ-preservation chemoradiotherapy studies

<table>
<thead>
<tr>
<th>Study</th>
<th>N</th>
<th>Neoadjuvant Chemo</th>
<th>Induction Chemo-XRT</th>
<th>Consolidation Chemo-XRT</th>
<th>Adjuvant Chemo</th>
<th>CR Rate (%)</th>
<th>CFS</th>
<th>OS</th>
</tr>
</thead>
<tbody>
<tr>
<td>RTOG 88-02</td>
<td>91</td>
<td>MCV</td>
<td>Cisplatin + once-daily XRT</td>
<td>Cisplatin + once-daily XRT</td>
<td>None</td>
<td>75</td>
<td>4 y: 44%</td>
<td>4 y: 62%</td>
</tr>
<tr>
<td>RTOG 89-03</td>
<td>61</td>
<td>MCV</td>
<td>Cisplatin + once-daily XRT</td>
<td>Cisplatin + once-daily XRT</td>
<td>None</td>
<td>59</td>
<td>5 y: 38%</td>
<td>5 y: 48%</td>
</tr>
<tr>
<td>RTOG 95-06</td>
<td>34</td>
<td>None</td>
<td>Cisplatin + 5FU + twice-daily XRT</td>
<td>Cisplatin + 5FU + twice-daily XRT</td>
<td>None</td>
<td>67</td>
<td>3 y: 66%</td>
<td>3 y: 83%</td>
</tr>
<tr>
<td>RTOG 97-06</td>
<td>47</td>
<td>None</td>
<td>Cisplatin + twice-daily XRT</td>
<td>Cisplatin + once-daily XRT</td>
<td>MCV</td>
<td>74</td>
<td>3 y: 48%</td>
<td>3 y: 61%</td>
</tr>
<tr>
<td>RTOG 99-06</td>
<td>81</td>
<td>None</td>
<td>Paclitaxel + cisplatin + twice-daily XRT</td>
<td>Paclitaxel + cisplatin + once-daily XRT</td>
<td>Gem + CP</td>
<td>81</td>
<td>5 y: 47%</td>
<td>5 y: 56%</td>
</tr>
<tr>
<td>RTOG 02-33</td>
<td>46</td>
<td>None</td>
<td>Paclitaxel + cisplatin + twice-daily XRT</td>
<td>Paclitaxel + cisplatin + twice-daily XRT</td>
<td>Gem + (CP or paclitaxel)</td>
<td>87</td>
<td>5 y: 67%</td>
<td>5 y: 71%</td>
</tr>
<tr>
<td>RTOG 02-33</td>
<td>47</td>
<td>None</td>
<td>Cisplatin + 5FU + twice-daily XRT</td>
<td>Cisplatin + 5FU + twice-daily XRT</td>
<td>Gem + (CP or paclitaxel)</td>
<td>79</td>
<td>5 y: 71%</td>
<td>5 y: 75%</td>
</tr>
</tbody>
</table>

Pooled results of above^1: 468 See above for RTOG 88-02 through RTOG 02-33

- **BC 2001**^3^: 182 Optional (31% received) 5FU + Mitomycin + once-daily XRT None 67 2 y: 88% 5 y: 48% | 178 Optional (34% received) None None 66 2 y: 83% 5 y: 35% |

- **RTOG 07-12**^2^: 32 None Cisplatin + 5FU + twice-daily XRT Cisplatin + 5FU + twice-daily XRT Gem + (CP or paclitaxel) Not available 32 None Low-dose Gem + once-daily XRT Low-dose Gem + once-daily XRT Gem + (CP or paclitaxel) Not available

Myths and Fears

- Poor Efficacy
- Cystectomy Complications
- Scarred non-functional bladder
How does Bladder Preservation compare to RC?

- Case control study of chemoRT age-matched to cystectomy patient from same institution
- 1998-2008, 66 patients, chemoRT worse comorbidity

Radical Cystectomy and TMT

5 year Overall Survival

- T2
- T3
- T4

MSKCC
USC
Switzerland
MGH
Radical Cystectomy and TMT

5 year Disease-Free Survival

- USC
- Switzerland
- MGH
<table>
<thead>
<tr>
<th>Treatment Comparison</th>
<th>Evidence</th>
<th>Level of evidence</th>
<th>Grade</th>
</tr>
</thead>
<tbody>
<tr>
<td>ChemoRT vs RT alone</td>
<td>Two RCTs report significant improvement in bladder tumor eradication.</td>
<td>1b</td>
<td>A</td>
</tr>
<tr>
<td>ChemoRT preserves good bladder function</td>
<td>Three QOL studies and RTOG protocols report good tolerance.</td>
<td>2a</td>
<td>B</td>
</tr>
<tr>
<td>Trimodality therapy vs immediate cystectomy</td>
<td>Comparison of three contemporary series of each treatment report similar 5- and 10-yr survival.</td>
<td>3</td>
<td>C</td>
</tr>
</tbody>
</table>

Myths and Fears

• Poor Efficacy

• Cystectomy Complications

• Scarred non-functional bladder
Immediate Post-ChemoRT Cystectomy

- 193 patients undergoing treatment naïve RC or RC after chemoRT (40 Gy w/ CDDP)

<table>
<thead>
<tr>
<th>Grade</th>
<th>Total (%)</th>
<th>CRT</th>
<th>No CRT</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>1</td>
<td>118 (61)</td>
<td>58 (67)</td>
<td>60 (57)</td>
<td>0.18</td>
</tr>
<tr>
<td>1</td>
<td>8 (4)</td>
<td>6 (7)</td>
<td>2 (2)</td>
<td>0.14</td>
</tr>
<tr>
<td>2</td>
<td>79 (41)</td>
<td>33 (38)</td>
<td>46 (43)</td>
<td>0.47</td>
</tr>
<tr>
<td>3a</td>
<td>21 (11)</td>
<td>13 (15)</td>
<td>8 (8)</td>
<td>0.06</td>
</tr>
<tr>
<td>3b</td>
<td>10 (5)</td>
<td>6 (7)</td>
<td>4 (4)</td>
<td>0.35</td>
</tr>
<tr>
<td>4 or 5</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td></td>
</tr>
</tbody>
</table>

Iwai Jpn J Clin Oncol 2011; 41: 1373.
# Salvage Cystectomy

<table>
<thead>
<tr>
<th></th>
<th>Patients</th>
<th>Overall Complications</th>
<th>Major Complications</th>
<th>Mortality</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hautmann</td>
<td>788</td>
<td>28%</td>
<td>n/a</td>
<td>5%</td>
</tr>
<tr>
<td>Stein</td>
<td>1054</td>
<td>28%</td>
<td>n/a</td>
<td>3%</td>
</tr>
<tr>
<td>Novara</td>
<td>358</td>
<td>49%</td>
<td>14%</td>
<td>3%</td>
</tr>
<tr>
<td>Bochner</td>
<td>18</td>
<td>33%</td>
<td>n/a</td>
<td>0%</td>
</tr>
<tr>
<td>Eisenberg</td>
<td>148</td>
<td>77%</td>
<td>32%</td>
<td>6%</td>
</tr>
<tr>
<td>Eswara</td>
<td>91</td>
<td>69%</td>
<td>16%</td>
<td>2%</td>
</tr>
</tbody>
</table>

### Long-term Toxicity of Bladder Preservation

<table>
<thead>
<tr>
<th></th>
<th>Gr3 GU</th>
<th>Gr4 GU</th>
<th>Gr3 GI</th>
<th>Gr4 GI</th>
</tr>
</thead>
<tbody>
<tr>
<td>Rodel</td>
<td>3%</td>
<td>2%</td>
<td>0%</td>
<td>2%</td>
</tr>
<tr>
<td>Efstathiou</td>
<td>6%</td>
<td>0%</td>
<td>2%</td>
<td>0%</td>
</tr>
<tr>
<td>Perdona</td>
<td>3%</td>
<td>1%</td>
<td>2%</td>
<td>0%</td>
</tr>
</tbody>
</table>

Rodel JCO 2002; 20:3061.
Perdona Cancer 2008;112:75.
Who Is Appropriate

• Primarily Indicated for Muscle Invasive
  – studies

• “Optimal candidates for bladder preservation with chemoradiation include patients with T2NX or N0M0 disease presenting without tumor-associated hydronephrosis, extensive CIS, or tumor invasion into the stroma of the prostate”

Primary Treatment for MIBC

With increasing age, use of RC falls – no concomitant increase in RT

Elderly Patients do well with Bladder Preservation

Mak JCO 2014; 32:3801.
Young Patients do well with Bladder Preservation

Mak JCO 2014; 32:3801.
Factors associated with DSS

<table>
<thead>
<tr>
<th>Univariate Comparison</th>
<th>HR</th>
<th>CI</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td>T2 v T3-4a</td>
<td>1.73</td>
<td>1.20-2.49</td>
<td>.0035</td>
</tr>
<tr>
<td>Urothelial vs other</td>
<td>1.03</td>
<td>0.45-2.35</td>
<td>.95</td>
</tr>
<tr>
<td>Low vs High grade</td>
<td>0.75</td>
<td>0.48-1.26</td>
<td>.30</td>
</tr>
<tr>
<td>Hydronephrosis</td>
<td>1.97</td>
<td>1.19-3.24</td>
<td>.008</td>
</tr>
<tr>
<td>Complete TURBT</td>
<td>1.79</td>
<td>1.07-2.97</td>
<td>.025</td>
</tr>
</tbody>
</table>

Mak JCO 2014; 32:3801.
Logistics of Bladder Preservation

- Aggressive TURBT
  - ≤ 6 weeks
- EBRT + Chemo
  - 6 wks – 3 mo
- Radical Cystectomy
- Cystoscopy ± Biopsies

LF
MGH/RTOG Split Course: Trimodality Therapy

1. Aggressive TURBT
2. 40-44 Gy + Chemo
3. Cystoscopy + Biopsies
4. 60-66 Gy total + Chemo
5. Radical Cystectomy

PR/NR

CR

3 wks
## Split versus Continuous

<table>
<thead>
<tr>
<th>End point</th>
<th>Split</th>
<th>Cont.</th>
<th>HRs</th>
<th>95% Cl</th>
<th>Abs. Benefit</th>
<th>HR</th>
</tr>
</thead>
<tbody>
<tr>
<td>OS</td>
<td>737/1346</td>
<td>1009/1793</td>
<td>0.940</td>
<td>0.816-1.084</td>
<td></td>
<td></td>
</tr>
<tr>
<td>CR</td>
<td>1009/1400</td>
<td>1344/1611</td>
<td>0.513</td>
<td>0.430-0.611</td>
<td>11.3%</td>
<td></td>
</tr>
<tr>
<td>BIS</td>
<td>323/723</td>
<td>504/1235</td>
<td>1.171</td>
<td>0.973-1.410</td>
<td></td>
<td></td>
</tr>
<tr>
<td>SC</td>
<td>287/1144</td>
<td>268/1416</td>
<td>1.435</td>
<td>1.188-1.732</td>
<td>5.7%</td>
<td></td>
</tr>
<tr>
<td>LF</td>
<td>222/825</td>
<td>443/1532</td>
<td>0.905</td>
<td>0.749-1.094</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Arcangeli Crit Reviews Oncol/Hematol 2015;94:105.
Role of Chemo During TMT

- Radiation sensitizer; systemic treatment

Table 1: The 5-yr overall survival and complete response rates from the University of Erlangen resulting from changes in therapeutic approach over the years [11-14]

<table>
<thead>
<tr>
<th>Treatment</th>
<th>Complete response</th>
<th>Overall survival</th>
</tr>
</thead>
<tbody>
<tr>
<td>RT alone</td>
<td>61%</td>
<td>40%</td>
</tr>
<tr>
<td>RT + carboplatin</td>
<td>66%</td>
<td>45%</td>
</tr>
<tr>
<td>RT + cisplatin</td>
<td>82%</td>
<td>62%</td>
</tr>
<tr>
<td>RT + cisplatin + 5-FU</td>
<td>87%</td>
<td>65%</td>
</tr>
</tbody>
</table>
Alternative Regimens

• Gemcitabine / Cisplatin –
  – Caffo Cancer 2011;117:1190
  – 26 patients; CCDP d1, 22; Gem weekly
  – 5yo OS 70%; IBS 74%

• MMC / 5FU – BC2001
  – 360 patients; MMC d1, bolus 5FU d 1, 16
  – 2y DFS 67%
Medical News Today

Immunotherapy breakthrough for advanced bladder cancer

After 30 years of no new medicine, finally hope for bladder cancer patients
New Directions

Radiation can increase antigen presentation and pro-inflammatory cytokines

Selective Bladder Preservation

• Ideal candidate:
  – Early stage, no hydronephrosis, complete initial resection
• Advantages:
  – Outpatient treatment
  – Majority of survivors will keep a functional bladder
• Disadvantages:
  – Requires close surveillance
  – May need cystectomy in future

Conclusions: For muscle invasive TCC, concurrent chemoradiation after aggressive transurethral resection provides similar survival as radical cystectomy and preserves functioning bladder. In the vast majority of patients.
Thank You