Multimodality Bladder Preservation: Curative Treatment and the Older Patient

Noam VanderWalde, MD
Assistant Professor, Radiation Oncology

8/8/2014
Disclosures

• I have no financial disclosures
The Treatment of Soft-tissue Sarcomas of the Extremities

Prospective Randomized Evaluations of (1) Limb-sparing Surgery Plus Radiation Therapy Compared with Amputation and (2) the Role of Adjuvant Chemotherapy

STEVEN A. ROSENBERG, M.D., Ph.D.; * JOEL TEPPER, M.D.; † ELI GLATSTEIN, M.D.; ‡ JOSE COSTA, M.D.; ‡
Agenda

• Older Patients and Patterns of Care

• Multimodality Treatment

• “Personalized” Medicine for Older Patients
Use of Radical Cystectomy for Patients With Invasive Bladder Cancer

John L. Gore, Mark S. Litwin, Julie Lai, Elizabeth M. Yano, Rodger Madison, Claude Setodji, John L. Adams, Christopher S. Saigal; the Urologic Diseases in America Project

- SEER-Medicare Analysis of >3000 patients
- 66 years and above
- Only 21% of patients received cystectomy

Gore et al. JNCI. 2010;102:2-10
Bladder Cancer: Practice Patterns

- National Cancer Data Base study of 28,691 patients with MIBC treated between 2004-2008 (excluded T4b, M1)
- Only 52.5% of patients received “aggressive therapy”

Gray et al Eur Urol 2013:63;823-829
Muscle-invasive bladder cancer: evaluating treatment and survival in the National Cancer Data Base

Angela B. Smith*, Allison M. Deal†‡, Michael E. Woods*, Eric M. Wallen*†,
• Frail/non-curative candidates?

• “Better guidelines are required for the selection of those patients >80 years of age who should or should not undergo radical cystectomy”

• “Bias runs deep in the urology community against RT for bladder cancer...the sense from the article...is that urologists are using the tools available to them but neglecting other tools that might be beneficial to their patients.”
Agenda

• Older Patients and Patterns of Care

• Multimodality Treatment

• “Personalized” Medicine and Older Patients
Selective Bladder Preservation

- Good pCR rates
- Good Cystectomy Free survival rates
- Good Overall Survival Rates

## Selective Bladder Preservation Studies

<table>
<thead>
<tr>
<th>Trial</th>
<th># Patients</th>
<th>Median Age/%≥60</th>
<th>pCR</th>
<th>Total RT dose</th>
<th>Survival</th>
<th>Bladder Intact</th>
</tr>
</thead>
<tbody>
<tr>
<td>Housset et al.¹ Paris</td>
<td>54</td>
<td>66/NS</td>
<td>67%</td>
<td>44 Gy</td>
<td>3y: 64%</td>
<td>NS</td>
</tr>
<tr>
<td>Kaufman et al.² MGH</td>
<td>53</td>
<td>66/NS</td>
<td>77%</td>
<td>64.8 Gy</td>
<td>5y: 48%</td>
<td>5 y among alive preserved: 89%</td>
</tr>
<tr>
<td>Shipley et al.³ RTOG 89-03</td>
<td>123</td>
<td>NS/75%</td>
<td>66%</td>
<td>64.8 Gy</td>
<td>5y: 48%</td>
<td>5 y among alive preserved: 72%</td>
</tr>
<tr>
<td>Kaufman et al.⁴ RTOG 95-06</td>
<td>34</td>
<td>NS/59%</td>
<td>67%</td>
<td>44 Gy</td>
<td>3y: 83%</td>
<td>3y: 66%</td>
</tr>
<tr>
<td>Hagan et al.⁵ RTOG 97-06</td>
<td>46</td>
<td>NS/68%</td>
<td>74%</td>
<td>64.8 Gy</td>
<td>3y: 61%</td>
<td>3y: 48%</td>
</tr>
<tr>
<td>Kaufman et al.⁶ RTOG 99-06</td>
<td>80</td>
<td>NS/72%</td>
<td>81%</td>
<td>64.3 Gy</td>
<td>5y: 56%</td>
<td>5y: 47%</td>
</tr>
</tbody>
</table>

¹Housett et al. JCO; Nov 1993:11(11):2150-2157
³Shipley et al. JCO; Nov 1998: 16(11): 3576-3583
⁴Kaufman et al. The Oncologist; 2000;5:471-476
⁵Hagan et al. IJROBP; 2003; 57(3):665-672
Combined secondary analysis of many of the previous studies

Median Age = 66.3 years

No patients required cystectomy due to toxicity.

75 and older

Disease-specific survival

Log-rank test: p = 0.6

Number at risk

<table>
<thead>
<tr>
<th>Followup time (years)</th>
<th>&lt;75 years old</th>
<th>&gt;75 years old</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>262</td>
<td>86</td>
</tr>
<tr>
<td>2</td>
<td>184</td>
<td>51</td>
</tr>
<tr>
<td>4</td>
<td>138</td>
<td>33</td>
</tr>
<tr>
<td>6</td>
<td>105</td>
<td>21</td>
</tr>
<tr>
<td>8</td>
<td>79</td>
<td>16</td>
</tr>
<tr>
<td>10</td>
<td>59</td>
<td>8</td>
</tr>
</tbody>
</table>

Correspondence with Efstathio, JA and Shipley, W. Data from MGH experience study
• Late Grade 3 GI toxicity: <6%  
• Late Grade 3 GU toxicity: <2%  
• Time to Grade 3 GU toxicity: 18.4 months  
• Time to Grade 3 GI toxicity: 25.8 months  
• Typically lasted ~7 months and did not persist  

Bladder Preservation in Older Patients

• Selective bladder approach
  – Requires patients eligible for cystectomy

• Cisplatinum based chemo regimens
  – Requires patients with good kidney function/hearing

• Complicated courses
  – Requires patients with good social support/transportation
# Definitive Bladder Sparing CRT trials

<table>
<thead>
<tr>
<th>Trial</th>
<th># Patients</th>
<th>Median Age</th>
<th>Total RT dose</th>
<th>cCR</th>
<th>Survival</th>
</tr>
</thead>
<tbody>
<tr>
<td>Shipley et al.¹</td>
<td>70</td>
<td>70 yrs</td>
<td>64.8 Gy (1.8) with Cis</td>
<td>77%</td>
<td>4y: 35%</td>
</tr>
<tr>
<td>NBCG 1987</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Hussain et al.²</td>
<td>56</td>
<td>67 yrs</td>
<td>60 Gy (2) With Cis and 5-FU</td>
<td>49%</td>
<td>5y: 32%</td>
</tr>
<tr>
<td>SWOG 2001</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>James et al.³</td>
<td>360</td>
<td>72 yrs</td>
<td>55 Gy (2.75) or 64 Gy (2) +/- 5-FU and mitomycin C</td>
<td>NS</td>
<td>5y CRT: 48%</td>
</tr>
<tr>
<td>BC2001 2012</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>5yr RT: 35%</td>
</tr>
</tbody>
</table>

¹Shipley et al. JAMA; Aug 1987; 258(7):931-935
²Hussain et al. J Urol; Jan 2001; 165: 56-61
³James et al. NEJM: Apr 2012; 366(16):1477-1488
• Phase 3 randomized study (2 x 2 design), 45 centers in UK
  – R1: +/- 5-FU mitomycin C (NON-CISPLATINUM REGIMEN)
  – R2: whole bladder or conedown (optional randomization)
• T2-4 N0M0 (different than SWOG and NCBG patients)
• Median Age: 72 years (closer to typical population)
• Primary end point locoregional disease free survival

A Locoregional Disease–free Survival

No. at Risk (no. of events)

<table>
<thead>
<tr>
<th></th>
<th>Chemoradiotherapy</th>
<th>Radiotherapy alone</th>
</tr>
</thead>
<tbody>
<tr>
<td>No. at Risk</td>
<td>182 (35)</td>
<td>178 (54)</td>
</tr>
<tr>
<td>No. at Risk (6 mos)</td>
<td>108 (14)</td>
<td>96 (16)</td>
</tr>
<tr>
<td>No. at Risk (12 mos)</td>
<td>76 (3)</td>
<td>69 (4)</td>
</tr>
<tr>
<td>No. at Risk (18 mos)</td>
<td>66 (1)</td>
<td>58 (1)</td>
</tr>
<tr>
<td>No. at Risk (24 mos)</td>
<td>56 (1)</td>
<td>44 (0)</td>
</tr>
<tr>
<td>No. at Risk (36 mos)</td>
<td>46 (1)</td>
<td>35 (1)</td>
</tr>
<tr>
<td>No. at Risk (48 mos)</td>
<td>25 (18)</td>
<td>18 (12)</td>
</tr>
</tbody>
</table>

Hazard ratio, 0.68 (95% CI, 0.48–0.96)
P=0.03
Overall Survival

Hazard ratio, 0.82 (95% CI, 0.63–1.09)
P=0.16

No. at Risk (no. of events)

<table>
<thead>
<tr>
<th></th>
<th>Chemoradiotherapy</th>
<th>Radiotherapy alone</th>
</tr>
</thead>
<tbody>
<tr>
<td>Months since Randomization</td>
<td></td>
<td></td>
</tr>
<tr>
<td>0</td>
<td>182 (35)</td>
<td>178 (35)</td>
</tr>
<tr>
<td>12</td>
<td>144 (33)</td>
<td>141 (34)</td>
</tr>
<tr>
<td>24</td>
<td>111 (11)</td>
<td>104 (17)</td>
</tr>
<tr>
<td>36</td>
<td>94 (9)</td>
<td>85 (15)</td>
</tr>
<tr>
<td>48</td>
<td>75 (3)</td>
<td>60 (7)</td>
</tr>
<tr>
<td>60</td>
<td>62 (1)</td>
<td>41 (2)</td>
</tr>
<tr>
<td>72</td>
<td>39</td>
<td>20</td>
</tr>
</tbody>
</table>
Chemoradiation for Bladder Cancer

• CRT can be a good alternative for non-cystectomy candidates

• Non-cystectomy candidates should be referred to a radiation oncologist and medical oncologist

• Frail/Not Chemo candidates?
Agenda

• Older Patients and Patterns of Care

• Multimodality Treatment

• “Personalized” Medicine and Older Patients
Personalized Care for Older Patients

• Staging their age and their cancer
  – Stage the patient’s functional status/functional age

• Determine candidacy for curative therapy?

• Guide which therapy?
Risk Score vs. KPS

Systemic Toxicity vs. Local Toxicity

• Systemic Toxicity ≠ Local Toxicity

• Local Toxicity for Cancer A ≠ Local Toxicity for Cancer B

• Bladder Specific Prospective Studies
HNC and Lung Cancer Study

Age ≥ 65
Cancer of the Head & Neck and Lung
Plan for curative radiotherapy or chemoradiotherapy

Consent
Baseline Assessments:
- CGA\(^1\)
- EORTC QLQ-C30\(^2\)
- PRO-CTCAE\(^3\)
- CTCAE\(^4\)
- Bloodwork\(^5\)

Radiation Treatment:
- Bi-Weekly Assessments: 5-7 weeks
- EORTC QLQ-C30\(^2\)
- PRO-CTCAE\(^3\)
- CTCAE\(^4\)

4-8 week post-treatment assessment:
- CGA\(^1\)
- EORTC QLQ-C30\(^2\)
- PRO-CTCAE\(^3\)
- CTCAE\(^4\)

\(^1\) Comprehensive Geriatric Assessment
\(^2\) EORTC QLQ-C30: European Organization for Research and Treatment of Cancer Quality of Life Questionnaire.
\(^3\) PRO-CTCAE: Patient Reported Outcomes of the Common Terminology Criteria for Adverse Events
\(^4\) CTCAE v4.02: Common Terminology Criteria for Adverse Events
\(^5\) p16\(^\text{INKa}\) collection from peripheral t-cells and baseline CBC.
Conclusion

• Bladder Cancer is a disease of older people

• Many older patients do not receive curative therapy

• ChemoRT is a good alternative to cystectomy for patients unable to undergo surgery

• Current and future studies of functional assessment may lead to improvement of care for older patients.