Bladder-Sparing Trimodality Therapy for Muscle-Invasive Bladder Cancer: Updates & Advances

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BCAN Think Tank
Denver, CO
August 12th, 2016
1. Organ conservation is commonplace in contemporary oncology

- Laryngeal carcinoma
- Anal carcinoma
- Breast carcinoma
- Esophageal carcinoma
- Limb sarcomas
Paradigm Shift in Multi-Modality Therapy for Invasive Cancers
Cystectomy is Life Altering
Two Standard CRT Methods of Bladder Preservation for MIBC

- **Maximal TURBT**
  - Split-course radiation
    - Induction chemoradiation (~40 Gy)
      - Cystoscopic re-biopsy for treatment response
        - Complete response
          - Consolidative chemoradiation (additional ~25 Gy)
          - Surveillance
        - Partial response (residual disease at cystoscopy)
          - Salvage therapy by cystectomy or best alternative
          - Surveillance
      - Muscle-invasive recurrence
  - Single-course radiation
    - Full-dose chemoradiation (55-65 Gy)
      - Cystoscopic re-biopsy for treatment response
        - Complete response
      - Surveillance

- Best alternative (by cystectomy or)

Bladder Conservation: Evolution of the MGH and RTOG approach

1986-93
Neoadjuvant chemo
Response evaluation
MCVx2
RT + C

1994-98
Accelerated radiation
Adjuvant chemotherapy
bidRT+C/5FU
MCV x 3

1999-2016
Enhanced Radiation sensitization
Adjuvant chemotherapy
bidRT+C/5FU or C/Tax
qdRT+Gem or 5FU/MMC
G + C x 4
2. Long-term results of TMT are excellent and comparable to RC

MGH Experience 1986-2013 (cT2-T4, n=475, f/u 7.2yrs)

<table>
<thead>
<tr>
<th></th>
<th>n</th>
<th>%</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Median Age</strong></td>
<td>67</td>
<td></td>
</tr>
<tr>
<td><strong>Sex</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Male</td>
<td>357</td>
<td>75%</td>
</tr>
<tr>
<td>Female</td>
<td>118</td>
<td>25%</td>
</tr>
<tr>
<td><strong>Clinical T Stage</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>cT2</td>
<td>317</td>
<td>67%</td>
</tr>
<tr>
<td>cT3</td>
<td>134</td>
<td>28%</td>
</tr>
<tr>
<td>cT4a</td>
<td>24</td>
<td>5%</td>
</tr>
<tr>
<td><strong>Hydronephrosis</strong></td>
<td>57</td>
<td>12%</td>
</tr>
<tr>
<td><strong>Carcinoma in situ</strong></td>
<td>116</td>
<td>24%</td>
</tr>
</tbody>
</table>

ASTRO 2015/GU ASCO 2016
Long-term results of TMT are excellent and comparable to RC

MGH Experience 1986-2013 (cT2-T4, n=475, f/u 7.2yrs)

<table>
<thead>
<tr>
<th></th>
<th>n</th>
<th>%</th>
</tr>
</thead>
<tbody>
<tr>
<td>Neoadjuvant Chemotherapy</td>
<td>118</td>
<td>25%</td>
</tr>
<tr>
<td>TURBT</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Visibly complete</td>
<td>333</td>
<td>70%</td>
</tr>
<tr>
<td>Visibly incomplete</td>
<td>142</td>
<td>30%</td>
</tr>
<tr>
<td>Response to induction chemoradiation</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Complete</td>
<td>357</td>
<td>75%</td>
</tr>
<tr>
<td>Incomplete</td>
<td>110</td>
<td>23%</td>
</tr>
<tr>
<td>Unknown</td>
<td>8</td>
<td>2%</td>
</tr>
</tbody>
</table>
## Improving CR Over Time

<table>
<thead>
<tr>
<th>Years Treated</th>
<th>Total No. Patients</th>
<th>No. with CR</th>
<th>% CR</th>
</tr>
</thead>
<tbody>
<tr>
<td>1986-1989</td>
<td>116</td>
<td>71</td>
<td>64.5%</td>
</tr>
<tr>
<td>1990-1993</td>
<td>64</td>
<td>42</td>
<td>67.7%</td>
</tr>
<tr>
<td>1994-1997</td>
<td>47</td>
<td>35</td>
<td>74.5%</td>
</tr>
<tr>
<td>1998-2001</td>
<td>85</td>
<td>64</td>
<td>75.3%</td>
</tr>
<tr>
<td>2002-2005</td>
<td>71</td>
<td>64</td>
<td>90.1%</td>
</tr>
<tr>
<td>2006-2009</td>
<td>49</td>
<td>44</td>
<td>89.8%</td>
</tr>
<tr>
<td>2010-2013</td>
<td>43</td>
<td>37</td>
<td>86.1%</td>
</tr>
</tbody>
</table>

- T2: 47%
- Hydronephrosis: 18%
- Complete TURBT: 60%
- T2: 93%
- Hydronephrosis: 3%
- Complete TURBT: 83%

ASTRO 2015/GU ASCO 2016
OS and DSS

Overall Survival

Disease-Specific Survival

5-year OS: 57%
10-year OS: 40%

5-year DSS: 66%
10-year DSS: 59%
DSS: Trimodality Therapy

Disease-Specific Survival

Log-rank test: $P < 0.0001$

Number at risk

<table>
<thead>
<tr>
<th></th>
<th>T3-4</th>
<th>T2</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>158</td>
<td>317</td>
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<tr>
<td>1</td>
<td>133</td>
<td>293</td>
</tr>
<tr>
<td>2</td>
<td>97</td>
<td>258</td>
</tr>
<tr>
<td>3</td>
<td>81</td>
<td>222</td>
</tr>
<tr>
<td>4</td>
<td>71</td>
<td>189</td>
</tr>
<tr>
<td>5</td>
<td>61</td>
<td>162</td>
</tr>
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<td>6</td>
<td>54</td>
<td>135</td>
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<td>7</td>
<td>48</td>
<td>119</td>
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<td>8</td>
<td>44</td>
<td>104</td>
</tr>
<tr>
<td>9</td>
<td>40</td>
<td>93</td>
</tr>
<tr>
<td>10</td>
<td>34</td>
<td>74</td>
</tr>
</tbody>
</table>
Clinicopathological stage discordance

T-Stage Discrepancy

Percent Discrepancy

- cT0/Tis/Ta: 33.7%
- cT1: 45.4%
- cT2: 46.2%
- cT3: 10.3% Upstaged, 9.1% Downstaged
- cT4: 20.8%

Gray et al. IJROBP 2014
DSS: Radical Cystectomy

Disease-Specific Survival

Long-term Cystectomy & PLND Results

- USC & U. Bern; 1985-2005; 959 patients
- pT2-3, cN0, cM0, median F/U 10 yrs

Contemporary results 2005-2013

Log-rank test: P = 0.0009

Disease-specific survival

Number at risk
1986-1995 208 184 149 135 120 106 96 85 80 75
1996-2004 158 139 119 97 83 74 65 61 57 51
2005-2013 109 103 87 71 57 43 28 21 11 7

Crude rate of cystectomy

Percent

1986-1995 38.9
1996-2004 20.3
2005-2013 14.7
Histologic Variants of Urothelial Carcinoma treated by TMT

DSS

OS

Log-rank test: P = 0.39

Log-rank test: P = 0.21

Krasnow et al. AUA 2016
3. Cystectomy is not being performed in 50% of patients – huge unmet need, TMT can fill the gap

ACS / National Cancer Database (2004-2008)
Long-term MGH Experience
Influence of Age

Disease-specific survival

Log-rank test: p = 0.6

Followup time (years)

Number at risk

<75 262 184 138 105 79 59
>75 86 51 33 21 16 8

<75 years old
>75 years old

Efstathiou et al Eur Urol 2012
Pooled RTOG MIBC studies – Disease-specific Survival for Age < 75 vs. Age ≥ 75

Mak et al. JCO 2014
4. Concurrent chemotherapy is important to the success of TMT

The active radiosensitizing drugs include:

- Cisplatin, Paclitaxel, 5-FU, Mitomycin C, Gemcitabine and tumor hypoxia-reducing drugs
BC2001: RCT RT +/- 5FU/MMC

2-yr LRDFS
67% (95% CI: 59%, 74%)  CT = 52/182
54% (95% CI: 46%, 62%)  No CT = 74/178

HR = 0.66 (95% CI: 0.46, 0.95); p = 0.02

James et al. NEJM 2012
RTOG PROTOCOL 02-33 (Randomized Phase II)
(PI: AL Zietman, MD)

Stage T2 – T4a, No Hydronephrosis
Candidate for cystectomy, if necessary

TURBT

randomization

bid RT
5FU
Cisplatin

bid RT
Taxol
Cisplatin

Finished accrual 2008
93 patients
RTOG 0233:
Overall survival by treatment arm

Mitin T, Hunt, D, Zietman, A et al. Lancet Oncol 2013
RTOG 0233:
Bladder-intact survival by treatment arm

Mitin T, Hunt, D, Zietman, A et al. Lancet Oncol 2013
RTOG PROTOCOL 07-12 (Randomized Phase II)

Stage T2 – T4a, No Hydronephrosis
Candidate for cystectomy, if necessary

TURBT

randomization

RTOG: bid RT 5FU Cisplatin

Michigan: qd RT Gemcitabine

Started accrual 2008, closed 2014
5. TURBT and Salvage Cystectomy key to success of TMT

Maximal Complete TURBT

Log-rank test: $P = 0.002$

Number at risk

<table>
<thead>
<tr>
<th>TURBT complete</th>
<th>332</th>
<th>301</th>
<th>263</th>
<th>221</th>
<th>194</th>
<th>165</th>
<th>143</th>
<th>124</th>
<th>109</th>
<th>97</th>
<th>76</th>
</tr>
</thead>
<tbody>
<tr>
<td>TURBT incomplete</td>
<td>138</td>
<td>120</td>
<td>88</td>
<td>78</td>
<td>63</td>
<td>55</td>
<td>43</td>
<td>40</td>
<td>36</td>
<td>33</td>
<td>29</td>
</tr>
</tbody>
</table>

Disease-specific survival vs. Follow-up time (years)
Salvage Cystectomy

- 129 patients (27%) underwent a salvage radical cystectomy
  - 65 for less than a CR to induction chemoradiation
  - 64 for superficial or muscle-invasive recurrences
  - One patient required RC for treatment-related toxicity
  - 5yr DSS 51% (if non-CR) and 64% (if later recurrence)
  - 15% salvage cystectomy in most recent era 2005-1013
Salvage Cystectomy

RTOG Pooled Analysis – Disease Specific Survival

Patients at risk: 100 85 66 50 45 41 34 30 17 13 8
Morbidity of primary radical cystectomy

1142 RCs at MSKCC 1995-2005

64% More than 1 complication
13% Grade 3-5
26% Readmissions
2% 90 day mortality

Donat et al Eur Urol 2009
Contemporary Cystectomy

• Randomized trial of robotic and open radical cystectomy
• 2/3 of patients in both arms had Grade 2-5 complications at 90 days.
• No difference by surgical technique

Bochner et al. Eur Urol 2015
Morbidity of salvage radical cystectomy at the MGH

<table>
<thead>
<tr>
<th>Grade</th>
<th>Total</th>
<th>&lt;30 days</th>
<th>&lt;90 days</th>
<th>MSKCC</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>72</td>
<td>53</td>
<td>58</td>
<td>26%</td>
</tr>
<tr>
<td>2</td>
<td>55</td>
<td>42</td>
<td>48</td>
<td>62%</td>
</tr>
<tr>
<td>3</td>
<td>52</td>
<td>11</td>
<td>18</td>
<td>11%</td>
</tr>
<tr>
<td>4</td>
<td>3</td>
<td>2</td>
<td>2</td>
<td>0%</td>
</tr>
<tr>
<td>5</td>
<td>2</td>
<td>2</td>
<td>2</td>
<td>2%</td>
</tr>
</tbody>
</table>

Eswara et al J Urol 2012
6. Superficial Recurrences can be managed conservatively

• 25% developed Non Muscle Invasive Tumors after Complete Response to TMT
• 60% recurrence free after TURBT and BCG
• Overall similar tolerability, toxicity, and outcomes compared to non-radiated patients

Sanchez, Wszolek, et al. AUA 2015
7. TMT can be considered for recurrent T1 bladder cancer

RTOG PROTOCOL 09-26 (Phase II)

Stage T1 G2 or G3, Failed intravesical therapy, Cystectomy next step

TURBT

Full dose RT
Concurrent cisplatin

Cystoscopic surveillance
8. The future is certainly promising

Stratification based on biomarkers

Laurberg et al., BJU Int. 2012
9. Bladder preservation with TMT is now supported by numerous guidelines

“Bladder preservation with chemotherapy and radiation is suitable for those who meet the specific requirements”
“In selected patients with MIBC, bladder-preserving therapy with cystectomy reserved for tumor recurrence represents a safe and effective alternative to immediate RC”
TMT Supported by NCCN Guidelines
TMT Supported by NCCN Guidelines

Bladder Cancer

- Neoadjuvant cisplatin-based combination chemotherapy followed by radical cystectomy (category 1)
- Bladder preservation following maximal TURBT with concurrent chemoradiotherapy
- Reassess tumor status 3 weeks after 40-45 Gy OR 2-3 months after full dose (60-65 Gy)
- Cystectomy (preferred)

- Reassess tumor status 2-3 months after treatment
- Observation
- Palliative TURBT and Best supportive care

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

- Negative nodes
  - Abdominal/pelvic CT or MRI if not previously done
  - Chest imaging
  - Bone scan if clinical suspicion or symptoms of bone metastases

- cT3, cT4a

- See Follow-up (BL-3)
10. Bladder preservation requires multidisciplinary teamwork

Massachusetts General Hospital

Rebecca H. Clayman
Jed S. Cheng
Michael Drumm
Alec Eidelman
Adam S. Feldman
Nicholas Giacalone
Pablo Gomery
Mukesh Harisinghani
Niall M. Heney
Douglas M. Dahl
Donald S. Kaufman
Richard J. Lee
Kimberley S. Mak
Frank J. McGovern
Dror M. Michaelson
Andrzej Niemierko
Aria Olumi
Michael L. Blute
Jon J. Paly
Hannah Roberts
William U. Shipley
Daphna Y. Spiegel
Matthew F. Wszolek
Chin-Lee Wu
Robin H. Young
Anthony L. Zietman
Many MIBC pts are not getting curative treatment
 undertreated and underserved population

TMT achieves CR and preserves the native bladder nowadays in up to 85% of patients, while offering long-term survival rates comparable to contemporary radical cystectomy series in selected patients

Long-term HRQOL of TMT is good

These results support such therapy as an acceptable alternative to cystectomy for selected patients (supported by EAU, NCCN, NICE guidelines)

Need to validate predictive biomarkers for personalized treatment selection and optimize concurrent and adjuvant therapies

Need continued multidisciplinary engagement and allow patient directed informed decision making