LA GESTIONE OTTIMALE DEL PAZIENTE CON CARCINOMA VESCICALE

Ferrara 30 ottobre 2015 •

Quale ruolo per la radioterapia

Dr. A. Stefanelli UOC Radioterapia oncologica
Bladder cancer

Non-muscle invasive bladder cancer (NMIBC)

Muscle invasive bladder cancer (MIBC) (T2-T4) on the other hand, represents a potentially grave danger, with long-term survival of approximately

T Staging for Bladder tumors

- Tx - Primary tumour cannot be assessed
- T0 - No evidence of primary tumour
- Ta - Non-invasive papillary carcinoma
- Tis - Carcinoma in situ: ‘flat tumour’
- T1 - Tumour invades subepithelial connective tissue
- T2 - Tumour invades muscle
  - T2a - Tumour invades superficial muscle (inner half)
  - T2b - Tumour invades deep muscle (outer half)
- T3 - Tumour invades perivesical tissue:
  - T3a - microscopically
  - T3b - macroscopically (extravesical mass)
- T4 - Tumour invades any of the following: prostate stroma, seminal vesicles, uterus, vagina, pelvic wall, abdominal wall
  - T4a - Tumour invades prostate stroma, seminal vesicles, uterus, or vagina
  - T4b - Tumour invades pelvic wall or abdominal wall

Cochrane Database Syst Rev 2002
Goals of Treatment

- Cure patient
- Optimize survival
- Prevention of Pelvic failure and Distant metastasis
- Functional Urinary reservoir and High Quality Of Life (QoL)
Radical cystectomy with urinary diversion has long been considered the standard of treatment for MIBC.
Contemporary series described 5-year overall survival rates of 45-67% with radical cystectomy alone with recurrence-free survival ranging from 62-71%
Radiotherapy (RT) is an alternative treatment with comparatively good results for those who are too frail to undergo cystectomy or for those who refuse operation.

**Table 1. Radiotherapy alone for invasive bladder cancer**

<table>
<thead>
<tr>
<th>Study</th>
<th>Patients (n)</th>
<th>Stage</th>
<th>Treatment (Gy)</th>
<th>3-to 5-year OS (%)</th>
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<tr>
<td>Moonen et al. (1998)</td>
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<td>64</td>
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<td>AF (60.8 Gy) n = 129</td>
<td>54 VS. 47</td>
<td></td>
</tr>
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<td></td>
<td></td>
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<td>CF (64 Gy) n = 100</td>
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<td></td>
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OS = overall survival, DSS = disease-specific survival, RT = radiotherapy, TUR = transurethral resection, AF = accelerated fractionation, CF = conventional fractionation.

Ann Oncol 2012
Strahlenther Onkol 2008
Patient who have RT are older

Patients who have RT have more advanced tumours.
Radical External Beam Radiation Therapy

- Historically, External Beam Radiation therapy was used as monotherapy for muscle invasive bladder cancer which were medically inoperable.
- 5-year local control rate:
  - 31% to 50% for the entire patient population
  - 49% to 79% for the subgroup of patients with a complete response

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Bladder Conservation approach

- 2 main concerns about bladder preservation compared with radical cystectomy:
  - *Toxicity of radiation therapy* on bladder function
  - *Field cancerization effect*:
    - 30-50% of patients experience a local recurrence (~50% invasive and ~50% superficial), either in the area of tumor or in a different part of bladder
    - If bladder preservation is selected, *close surveillance is critical*
No trials have till date directly compared Cystectomy and Bladder-preservation
Trimodality Therapy

– Combination of Limited Resection, Chemotherapy, and Irradiation in Bladder Preservation
  • Best results till date in bladder preservation when the 3 modalities are combined together
  • Based on both single institutional data and large randomised control trials
PIONEERING SINGLE INSTITUTION STUDIES OF TRIMODALITY TREATMENT

**MGH**

- TURBT
  - RT + CHT (Induction)
    - Restaging cystoscopy
      - Complete Response
      - Incomplete Response
    - RT + CHT (Consolidation)
      - Cystectomy

**ERLANGEN**

- TURBT
  - RT + CHT (Whole treatment)
    - Restaging cystoscopy
      - Complete Response
      - Incomplete Response
    - FU
      - Cystectomy
      - NED
      - Recurrence
      - FU
        - Recurrence
        - Cystectomy
Long-Term Outcomes of Selective Bladder Preservation by Combined-Modality Therapy for Invasive Bladder Cancer: The MGH Experience

**Table 1 – Protocol design and treatment**

<table>
<thead>
<tr>
<th>Protocol</th>
<th>Neoadjuvant chemotherapy</th>
<th>Induction or concurrent</th>
<th>Response</th>
<th>Consolidation or cystectomy</th>
<th>Adjuvant chemotherapy</th>
<th>Patients, no. (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>MGH 180</td>
<td>MCV</td>
<td>CP + RT</td>
<td>CR</td>
<td>CP + RT</td>
<td>None</td>
<td>50 (14.4)</td>
</tr>
<tr>
<td>MGH 880, RTOG 89-03 Arm 1</td>
<td>MCV</td>
<td>CP + RT</td>
<td>IR CR</td>
<td>Cystectomy</td>
<td>None</td>
<td>56 (55.4)</td>
</tr>
<tr>
<td>MGH 880, RTOG 89-03 Arm 2</td>
<td>None</td>
<td>CP + RT</td>
<td>IR CR IR</td>
<td>Cystectomy</td>
<td>None</td>
<td>45 (44.6)</td>
</tr>
<tr>
<td>MGH 930A</td>
<td>None</td>
<td>CP + 5FU + BID RT</td>
<td>CR</td>
<td>CP + 5FU + BID RT</td>
<td>MCV 3 cycles</td>
<td>21 (6.0)</td>
</tr>
<tr>
<td>RTOG 95-06</td>
<td>None</td>
<td>CP + 5FU + BID RT</td>
<td>IR CR</td>
<td>Cystectomy</td>
<td>None</td>
<td>14 (4.0)</td>
</tr>
<tr>
<td>RTOG 97-06</td>
<td>None</td>
<td>CP + BID RT</td>
<td>IR CR IR</td>
<td>Cystectomy</td>
<td>MCV 3 cycles</td>
<td>22 (6.3)</td>
</tr>
<tr>
<td>RTOG 99-06</td>
<td>None</td>
<td>CP + Taxol + BID RT</td>
<td>CR</td>
<td>CP + Taxol + BID RT</td>
<td>CP + Gem 4 cycles</td>
<td>45 (12.9)</td>
</tr>
<tr>
<td>Per protocol</td>
<td>Varied</td>
<td>Varied</td>
<td>IR CR IR</td>
<td>Cystectomy</td>
<td>Varied</td>
<td>95 (27.3)</td>
</tr>
</tbody>
</table>

Total: 348

MGH = Massachusetts General Hospital; MCV = methotrexate, cisplatin, vinblastine; CP = cisplatin; RT = radiation therapy; CR = complete response; IR = incomplete response; RTOG = Radiation Therapy Oncology Group; 5FU = 5-fluorouracil; BID = twice daily; Gem = gemcitabine.
low incidence of late pelvic toxicity in patients retaining their bladder (late grade 3 genitourinary and GI toxicity in 5.7% and 1.9% of patients, respectively)
# Long-Term Outcomes of Selective Bladder Preservation by Combined-Modality Therapy for Invasive Bladder Cancer: The MGH Experience

## Table 4 - Univariate Cox regression analyses for survival end points

<table>
<thead>
<tr>
<th>Covariates</th>
<th>Comparison</th>
<th>OS</th>
<th></th>
<th>DSS</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>HR</td>
<td>p</td>
<td>95% CI</td>
<td>HR</td>
</tr>
<tr>
<td>Age, yr</td>
<td>&gt;65 vs. ≤65</td>
<td>1.41</td>
<td>0.013</td>
<td>1.07–1.85</td>
<td>0.92</td>
</tr>
<tr>
<td>Gender</td>
<td>Male vs female</td>
<td>1.06</td>
<td>0.72</td>
<td>0.79–1.42</td>
<td>1.12</td>
</tr>
<tr>
<td>Clinical stage</td>
<td>T2 vs T3/T4</td>
<td>0.59</td>
<td>0.001</td>
<td>0.45–0.77</td>
<td>0.53</td>
</tr>
<tr>
<td>Complete TURBT</td>
<td>Yes vs no</td>
<td>0.67</td>
<td><strong>0.003</strong></td>
<td>0.51–0.88</td>
<td>0.67</td>
</tr>
<tr>
<td>Hydronephrosis</td>
<td>Yes vs no</td>
<td>1.79</td>
<td><strong>&lt;0.001</strong></td>
<td>1.29–2.47</td>
<td>2.08</td>
</tr>
<tr>
<td>Induction response</td>
<td>Complete vs incomplete</td>
<td>0.49</td>
<td><strong>0.001</strong></td>
<td>0.37–0.65</td>
<td>0.37</td>
</tr>
<tr>
<td>Neoadjuvant chemotherapy</td>
<td>Yes vs no</td>
<td>1.03</td>
<td>0.22</td>
<td>0.78–1.35</td>
<td>0.99</td>
</tr>
<tr>
<td>Radiation fractionation</td>
<td>BID vs QD</td>
<td>0.86</td>
<td>0.30</td>
<td>0.64–1.15</td>
<td>0.94</td>
</tr>
<tr>
<td>Cystectomy</td>
<td>Delayed vs immediate</td>
<td>0.76</td>
<td>0.23</td>
<td>0.48–1.20</td>
<td>0.60</td>
</tr>
<tr>
<td></td>
<td>Any vs none</td>
<td>1.41</td>
<td><strong>0.014</strong></td>
<td>1.07–1.87</td>
<td>1.69</td>
</tr>
</tbody>
</table>

OS = overall survival; DSS = disease-specific survival; HR = hazard ratio; CI = confidence interval; TURBT = transurethral resection of bladder tumor; BID = twice daily; QD = once daily.
PIONEERING SINGLE INSTITUTION STUDIES OF TRIMODALITY TREATMENT

overall and disease-specific survival rates were 51% and 56% at 5 years, and 31% and 42% at 10 years, respectively, and more than 80% of survivors preserved their intact, well-functioning bladder (cystectomy as a result of a contracted bladder was restricted to 2% of patients)
A recent systematic review of all available retrospective and prospective series and studies of TMT for muscle-invasive bladder cancer confirmed cancer specific and overall survival rates in the range of 50% to 82% and 36% to 74%, respectively, with salvage cystectomy restricted to 25% to 30% of patients.
Trimodality Treatment

• Ideal candidates for Bladder preservation with Trimodality treatment:
  – Solitary T2 or early T3 tumors < 6 cm
  – No tumor-associated hydronephrosis
  – Tumors allowing a visibly complete TURBT
  – Invasive tumors not associated with extensive carcinoma in situ
  – Adequate renal function to allow cisplatin concurrent with radiation
  – TCC histology
  – Willing for being on close surveillance
  – Willing for cystectomy in case of progression or relapse
Those involved in the management of muscle invasive bladder cancer should “take a leaf from the book” on sarcoma and breast cancer management, where multidisciplinary collaborative approach with knowledge and respect for the benefits and shortcomings of individual treatment modalities has led to a standard of organ preservation.
## SURVIVAL DATA OF RADICAL CYSTECTOMY AND SELECTIVE BLADDER PRESERVATION

<table>
<thead>
<tr>
<th>Series</th>
<th>Year</th>
<th>Category</th>
<th>No. Patients</th>
<th>5-yr Survival</th>
<th>10-yr Survival</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cystectomy</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>USC</td>
<td>2001</td>
<td>pT2-pT4a</td>
<td>633</td>
<td>48%</td>
<td>32%</td>
</tr>
<tr>
<td>MSKCC</td>
<td>2001</td>
<td>pT2-pT4a</td>
<td>181</td>
<td>36%</td>
<td>27%</td>
</tr>
<tr>
<td>SWOG/ECOG/CALGB†</td>
<td>2002</td>
<td>cT2-cT4a</td>
<td>317</td>
<td>49%</td>
<td>34%</td>
</tr>
<tr>
<td>Selective Bladder Preservation</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>University of Erlangen†</td>
<td>2002</td>
<td>cT2-cT4a</td>
<td>326</td>
<td>45%</td>
<td>29%</td>
</tr>
<tr>
<td>MGH</td>
<td>2009</td>
<td>cT2-cT4a</td>
<td>348</td>
<td>52%</td>
<td>35%</td>
</tr>
<tr>
<td>RTOG</td>
<td>1998</td>
<td>cT2-cT4a</td>
<td>123</td>
<td>49%</td>
<td>—</td>
</tr>
</tbody>
</table>
7.4 Radical surgery and urinary diversion
7.4.1 Removal of the tumour-bearing bladder
7.4.1.1 Introduction

Radical cystectomy is the standard treatment for localised MIBC in most Western countries [164, 226]. Recent interest in patients’ quality of life (QoL) has promoted the trend toward bladder-preserving treatment modalities, such as radio- and/or chemotherapy (see Sections 7.2 and 7.6). Performance status (PS) and age influence the choice of primary therapy, as well as the type of urinary diversion, with cystectomy being reserved for younger patients without concomitant disease and with a better PS. The value of assessing overall health before recommending and proceeding with surgery was emphasised in a multivariate analysis [136]. The analysis found an association between comorbidity and adverse pathological and survival outcome following radical cystectomy [136]. Performance status and comorbidity have a different impact on treatment outcomes and must be evaluated independently [142].
221 patients, T2-4Nx-0M0 bladder cancer, Treated on protocols 1986-2000, median follow up: 6.3 years
Urodynamic study, QOL questionnaire

- 78% have compliant bladders with normal capacity and flow parameters
- 85% have no urgency or occasional urgency
- 25% have occasional to moderate bowel control symptoms
- 50% of men have normal erectile function
157 patients with Bladder Preservation who survived 2 to 13 years (Median follow-up - 5.2 years)

22% - Grade 1

10% - Grade 2

7% - Grade 3 (5.7% GU, 1.9% GI)

0% - Grade 4

0% - Grade 5
Modalities of External Beam Radiation Therapy

- 2D Conventional
- 3D Conformal Radiation therapy
- Intensity Modulated Radiation Therapy (IMRT)
- VMAT
- Adaptive RT (ART)
IMRT technique
ADAPTIVE RADIOThERAPy Image Guidance

Planning CT

Week 1

Week 2

Week 3

ADAPTIVE RADIOThERAPy A Need for ART

Daily Bladder Volume

Bladder Volume (cc)

Treatment Fraction

0 50 100 150

0 4 9 14 19 24 29
Conclusions

• Combined modality therapy achieves a complete response and preserves the native bladder in ~70% of patients, while offering long-term survival rates comparable to contemporary radical cystectomy series.

• QoL studies have demonstrated that the retained native bladder functions well and long-term toxicity of chemo irradiation to pelvic organs is relatively low.

• These results support the acceptance of modern bladder-sparing Trimodality therapy for selected patients as a proven alternative to cystectomy.
Conclusions

• The optimal regimen of combined chemo irradiation, as well as the addition of rational molecular targeted therapy and personalized treatment selection, continues to be investigated.

• The contribution of selective bladder sparing therapy to the quality of life of patients represents a unique opportunity for urologic surgeons, radiation oncologists, and medical oncologists to work hand in hand in a truly multidisciplinary effort.

• Role of new radiation techniques.