Combined Modality, Organ Sparing Approaches for Muscle Invasive Urothelial Cancer

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Radical Cystectomy (outcomes)
No Chemotherapy

A

B

Madersbacher S et al. JCO 2003;21:690-696

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### Table 2. Local Recurrence and Distant Failure According to Tumor Stage

<table>
<thead>
<tr>
<th>Tumor Stage</th>
<th>NED</th>
<th>Local Recurrence</th>
<th>Distant Failure</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>No.</td>
<td>%</td>
<td>No.</td>
</tr>
<tr>
<td>pTa/pTis/pT1pN0 (n = 92)</td>
<td>66</td>
<td>72</td>
<td>2</td>
</tr>
<tr>
<td>All pTis/pT1pN0-2 (n = 94)</td>
<td>67</td>
<td>71</td>
<td>2</td>
</tr>
<tr>
<td>pT2pN0 (n = 125)</td>
<td>91</td>
<td>73</td>
<td>4</td>
</tr>
<tr>
<td>All pT2pN0-2 (n = 151)</td>
<td>105</td>
<td>69</td>
<td>6</td>
</tr>
<tr>
<td>pT3pN0 (n = 120)</td>
<td>67</td>
<td>56</td>
<td>9</td>
</tr>
<tr>
<td>All pT3pN0-2 (n = 184)</td>
<td>91</td>
<td>49</td>
<td>16</td>
</tr>
<tr>
<td>pT4pN0 (n = 46)</td>
<td>20</td>
<td>43</td>
<td>9</td>
</tr>
<tr>
<td>All pT4pN0-2 (n = 78)</td>
<td>25</td>
<td>32</td>
<td>16</td>
</tr>
<tr>
<td>Organ confined (≤pT2pN0; n = 217)</td>
<td>157</td>
<td>72</td>
<td>6</td>
</tr>
<tr>
<td>Non-organ confined (&gt;pT2pN0; n = 166)</td>
<td>87</td>
<td>52</td>
<td>18</td>
</tr>
<tr>
<td>All pN+ (n = 124)</td>
<td>44</td>
<td>36</td>
<td>16</td>
</tr>
<tr>
<td>Total (n = 507)</td>
<td>288</td>
<td>56</td>
<td>40</td>
</tr>
</tbody>
</table>

Abbreviation: NED, no evidence of disease.
Management of T2 disease

N -

- Cystectomy
- Neoadjuvant chemo
- Radiation + Chemo ( +/- neoadjuvant chemo)
- Maximal TURBT + RT

N+

- Chemotherapy followed by local treatment if NED (cysto)
Organ Preservation in Muscle Invasive Disease
Trimodality Approach

TURBT

Induction irradiation and concurrent chemotherapy

Repeat cystoscopy with transurethral biopsy

Complete response

Consolidation chemotherapy and irradiation ± adjuvant chemotherapy AND long-term cystoscopic surveillance

Incomplete response

Radical cystectomy ± adjuvant chemotherapy

Recurrent tumor
Fig 1. Arm 1 of RTOG 89-03 for the treatment of invasive bladder cancer with combined TURBT, chemotherapy, and radiation therapy for attempted bladder preservation.
Organ Preservation
CMV + RT/DDP

DSS

OS

Shipley et al 2002
## Selective Organ Preservation
Shipley et al 2002

<table>
<thead>
<tr>
<th>Patient Group</th>
<th>n</th>
<th>Overall Survival (%)</th>
<th>Disease-Specific Survival (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>5 yr</td>
<td>10 yr</td>
</tr>
<tr>
<td>All patients</td>
<td>190</td>
<td>54 ± 7.5*</td>
<td>36 ± 8.3*</td>
</tr>
<tr>
<td>Age at entry</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>(yr)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>&lt;75</td>
<td>155</td>
<td>55</td>
<td>40</td>
</tr>
<tr>
<td>&gt;75</td>
<td>35</td>
<td>51</td>
<td>22</td>
</tr>
<tr>
<td>Sex</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Female</td>
<td>47</td>
<td>59</td>
<td>40</td>
</tr>
<tr>
<td>Male</td>
<td>143</td>
<td>52</td>
<td>34</td>
</tr>
<tr>
<td>Clinical stage</td>
<td></td>
<td></td>
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</tr>
<tr>
<td>T2</td>
<td>90</td>
<td>62</td>
<td>41</td>
</tr>
<tr>
<td>T3-T4a</td>
<td>10</td>
<td>47</td>
<td>31</td>
</tr>
<tr>
<td>Hydronephrosis</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>No</td>
<td>163</td>
<td>55</td>
<td>37</td>
</tr>
<tr>
<td>Yes</td>
<td>27</td>
<td>48</td>
<td>29</td>
</tr>
</tbody>
</table>
Long-term disease-specific survival with selective bladder preservation from the Massachusetts General Hospital experience

![Graph showing disease-specific survival over time with percentage drops for different tumor stages (cT2, cT3−T4a) and number at risk table below. Log-rank test: p = 0.0004.](image-url)
Radiotherapy with or without Chemotherapy in Muscle-Invasive Bladder Cancer
Nicholas D. James, M.B., B.S., Ph.D for the BC2001 Investigators*

- Histologically confirmed stage T2, T3, or T4a bladder cancer (adenocarcinoma or transitional or squamous-cell carcinoma) with no signs of lymph-node involvement or metastasis.

- 55 Gy in 20 fractions over a 4-week period or 64 Gy in 32 fractions over a 6.5-week period.

- Fluorouracil by continuous infusion (500 mg/m2 per day) during fractions 1 to 5 and 16 to 20 of radiotherapy. Mitomycin C 12 mg/m2 IV on day 1.

There was a trend toward an increased rate of salvage cystectomy in the radiotherapy alone group:

→ (20 patients in the chemo-radiotherapy group vs. 31 in the radiotherapy group) for a hazard ratio of 0.58 (95% CI, 0.33 to 1.03; P = 0.07)
Bladder Preservation
Not a good option

- Tumor > 5 cm
- Hydronephrosis/poor renal function
- Multifocal disease
- Poor bladder function/incontinence
- Carcinoma in situ (CIS)
- Very large/advanced tumors (T4 or T3b disease/N+)
Although most completely responding patients retain their bladders free from invasive relapse, one quarter will develop superficial disease.

Zietman AL et al, Urology 58(3),380-385,2001
Should Patients managed with organ preservation receive neo adjuvant chemotherapy?
RTOG 89-03

Results

- **5-yr actuarial OS:** 48% vs 49% (not SS)
- **5-yr survival rate with functioning bladder:** 36% vs 40% (not SS)

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**Fig 3.** Overall survival rates for patients randomized to neoadjuvant MCV chemotherapy on arm 1 compared with those randomized to no MCV (arm 2).

**Fig 4.** Patient survival rate with an intact bladder for patients randomized to receive neoadjuvant MCV chemotherapy or no MCV chemotherapy on RTOG 89-03.
RTOG 89-03:
RT+DDP +/- neoadjuvant MCV

123 pts T2-4NxMo post TURBT randomized to RT+DDP with or without neoadjuvant MCV:

- Distant mets: 33% vs. 39% N.S.
- 5-year survival: 48% vs. 49% N.S.

However:
67% completed protocol on the neoadjuvant arm

Numbers too small for reliable conclusions.
# Neo Adjuvant Chemotherapy

<table>
<thead>
<tr>
<th>Study</th>
<th>N</th>
<th>Randomization</th>
<th>Result</th>
</tr>
</thead>
</table>
| SWOG 8710 (INT0800)    | 317| MVAC x3 → surgery v surgery alone                 | • Improved OS with MVAC (77 v 46 months; P=0.05)  
• Improved rate of pT0 disease with MVAC (38% v 15%; P<0.001) |
| BA063984               | 976| CMV x3 → surgery/radiation v surgery/radiation alone | • Improvement in 10-year survival with CMV (36% v 30%), translating to a 16% reduction in the risk of death |
FIGURE 6 Survival among patients randomly assigned to receive methotrexate, vinblastine, doxorubicin, and cisplatin (MVAC) followed by cystectomy or cystectomy alone, according to an intention-to-treat analysis

SWOG 8710

Herr H W et al. JCO 2004;22:2781-2789
**Figure 2.** Survival According to Treatment Group and Whether Patients Were Pathologically Free of Cancer (pT0) or Had Residual Disease (RD) at the Time of Cystectomy.

M-VAC denotes methotrexate, vinblastine, doxorubicin, and cisplatin, and NR not reached.
BA6 Study
Kaplan-Meier curves for (A) overall survival, (B) metastasis-free survival, (C) locoregional disease-free survival, and (D) disease-free survival.

International Collaboration of Trialists on behalf of the Medical Research Council Advanced Bladder Cancer Working Party (now the National Cancer Research Institute Bladder Cancer Clinical Studies Group), the European Organisation for Research and Treatment of Cancer Genito-Urinary Tract Cancer Group, the Australian Bladder Cancer Study Group, the National Cancer Institute of Canada Clinical Trials Group, Finnblander, Norwegian Bladder Cancer Study Group, and Club Urologico Espanol de Tratamiento Oncologico Group JCO 2011;29:2171-2177

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Overall survival in patients who received (A,C) radiotherapy only and (B,D) cystectomy only.
Results

### Table 1

<table>
<thead>
<tr>
<th>Endpoint</th>
<th>Chemotherapy type</th>
<th>Number of patients/events</th>
<th>HR (95% CI)</th>
<th>Effect p-value</th>
<th>Absolute benefit at 5 yrs (95% CI)</th>
<th>Interaction p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Overall survival</td>
<td>Single agent platinum</td>
<td>261/376</td>
<td>1.15 (0.90–1.47)</td>
<td>0.26</td>
<td>−5% (−14% to 4%)</td>
<td>0.029</td>
</tr>
<tr>
<td></td>
<td>Platinum based combinations</td>
<td>1430/2433</td>
<td>0.86 (0.77–0.95)</td>
<td>0.003</td>
<td>5% (2% to 9%)</td>
<td></td>
</tr>
<tr>
<td></td>
<td>All trials</td>
<td>1691/2890</td>
<td>0.89 (0.81–0.98)</td>
<td>0.022</td>
<td>4% (0% to 7%)</td>
<td></td>
</tr>
<tr>
<td>Disease-free survival</td>
<td>Single agent platinum</td>
<td>166/217</td>
<td>1.14 (0.83–1.55)</td>
<td>0.42</td>
<td>−5% (−16% to 7%)</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Platinum based combinations</td>
<td>1681/2629</td>
<td>0.78 (0.71–0.86)</td>
<td>&lt;0.0001</td>
<td>9% (5% to 12%)</td>
<td>0.024</td>
</tr>
<tr>
<td></td>
<td>All trials</td>
<td>1847/2846</td>
<td>0.81 (0.74–0.89)</td>
<td>&lt;0.0001</td>
<td>8% (4% to 11%)</td>
<td></td>
</tr>
</tbody>
</table>

Fig. 2. Overall survival curve (platinum based combination chemotherapy trials only).
Fig 3. Disease-free survival distributions of patients with a bladder who had bladder-sparing surgery after achieving T0 status to MVAC chemotherapy. TUR, 28 patients, 17 censored who did not die of disease or have salvage cystectomy; PC, 15 patients, 8 censored.
Neo adjuvant + Adjuvant M-VAC vs. Adjuvant M-VAC only after Radical Cystectomy

MD Anderson

Millikan R et al. JCO 2001;19:4005-4013
Chemo + RT
With or without neo adjuvant ChemoRx

Neo adjuvant + chemo Rx + RT

Neo Adjuvant Chemo Rx + surgery for responders (if Resectable);
RT probably palliative (except CRs?)
3D-Radiation Treatment Fields

- Simulated supine with immobilization and empty bladder
- Initial treatment 4-field box technique to include the entire bladder, prostate (or proximal vagina) and pelvic LNs
- Treated to 39.6 Gy/1.8 Gy fx with concurrent cisplatin 100 mg/m² days 1 and 22
- 4 week break with urologic restaging that included exam under anesthesia, cystoscopy with tumor site biopsy and urine cytology
- If not CR → radical cystectomy
- If CR → consolidative RT with add’l 25.2 Gy for total of 64.8 Gy to bladder tumor volume and a 3rd dose of cisplatin 100 mg/m² given on first day of treatment
Dosimetry
Biomarker Directed Bladder CA Rx: The p53 story

- Major pathways for bladder cancer pathogenesis:
  - p53
  - Rb
  - EGFR/Her2 (RAS-MAPK pathways)

- The *TP53* or p53 pathway is the most commonly dysregulated pathway in bladder cancer.
  - Retrospective data suggested p53 alteration was prognostic and predictive for cisplatin based treatment
  - However, a recent phase III trial of p53-directed MVAC treatment in T1/T2N0 bladder cancer was negative (Stadler et. al. JCO 2012)
Prediction of pathologic complete response to neoadjuvant chemotherapy in urothelial cancer by genetic determinants of platinum sensitivity. (ASCO GU 2013)

Peter H. O'Donnell, Shaheen Alanee, Hongyuan Cao, Irina Ostrovnaya, Ilana Rebecca Garcia-Grossman, Cory Ganshert, Norm D. Smith, Gary D. Steinberg, Kenneth Offit, Walter Michael Stadler and Dean F. Bajorin

The University of Chicago, Chicago, IL; Memorial Sloan-Kettering Cancer Center, New York, NY

rs244898 in RARS (odds ratio [OR] 6.8 [95% CI 1.6-32.6], P=0.01) and rs7937567 in GALNTL4 (OR 5.2 [95% CI 1.1-26.2], P=0.03) were associated with likelihood of achieving pT0
Future Directions:
Targeted Therapies for Bladder CA

<table>
<thead>
<tr>
<th>Target</th>
<th>Agent</th>
<th>Phase</th>
<th>Trial</th>
</tr>
</thead>
<tbody>
<tr>
<td>EGFR</td>
<td>Gefitinib</td>
<td>II (Gem/Cis)#</td>
<td>CALGB 90102</td>
</tr>
<tr>
<td>EGFR</td>
<td>Cetuximab</td>
<td>II (Gem/Cis)</td>
<td>NCT00645593</td>
</tr>
<tr>
<td>Her2/Neu</td>
<td>Trastuzumab</td>
<td>II (Gem/Cis)</td>
<td>NCT01828736</td>
</tr>
<tr>
<td>Her2/Neu</td>
<td>Trastuzumab</td>
<td>I/II (Paclitaxel + XRT)</td>
<td>RTOG 0524</td>
</tr>
<tr>
<td>VEGFR/PDGFR/RAF</td>
<td>Sorafenib</td>
<td>II (Gem/Cis)#</td>
<td>AUO-AB 31/05</td>
</tr>
<tr>
<td>VEGF</td>
<td>Bevacizumab</td>
<td>III (Gem/Cis)</td>
<td>NCT00942331</td>
</tr>
<tr>
<td>VEGFR/EGFR</td>
<td>Vandetanib</td>
<td>II (Gem/Carbo)</td>
<td>NCT01191892</td>
</tr>
<tr>
<td>VEGFR/PDGFR</td>
<td>Sunitinib</td>
<td>II (Gem/Cis)</td>
<td>NCT01089088</td>
</tr>
<tr>
<td>VEGFR</td>
<td>Pazopanib</td>
<td>II</td>
<td>INT70/09</td>
</tr>
</tbody>
</table>

# - negative randomized phase II or compared to historical control
Future Directions: Bladder Cancer Stem Cells?

- Populations of CD44+CK5+CK20- cells isolated from human bladder cancers are tumor initiating cells (TICs) in mouse xenografts and can give rise to CD44+ and CD44- tumor populations after multiple serial transplantations.
- Bladder cancer TICs (aka cancer stem cells) share cell surface markers similar to bladder basal cells, e.g. CD44+ and CK5+.
- Bladder cancer stem cells preferentially overexpress CD47 which prevents macrophage phagocytosis.
- Blocking anti-CD47 antibodies induced macrophage phagocytosis and elimination of bladder cancer stem cells in vitro.
**Clinical Staging**

**Primary Treatment**
- Radical cystectomy\(^b\) and consider neoadjuvant cisplatin-based combination chemotherapy (category 1)
- Segmental (partial) cystectomy\(^b\) (highly selected patients with solitary lesion in a suitable location; no Tis) and consider neoadjuvant cisplatin-based combination chemotherapy\(^m\)
- Bladder preservation\(^b\) following maximal TURBT with concurrent chemotherapy\(^m\) + RT\(^n\) (category 2B)\(^c\)

**ADjuvant Treatment**
- Consider adjuvant chemotherapy\(^m\) (category 2B) based on pathologic risk (pT3-4, positive nodes) if no neoadjuvant treatment given
- Consider adjuvant RT\(^n\) (category 2B) or chemotherapy\(^m\) (category 2B) based on pathologic risk (pT3-4, positive nodes, positive margin, high-grade) if no neoadjuvant treatment given

**Follow-up**
- Observation or completion of RT\(^n\) up to 66 Gy and consider adjuvant chemotherapy\(^m\) (category 2B)

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\(^b\)See Principles of Surgical Management (BL-A).
\(^c\)The modifier "c" refers to clinical staging based on bimanual examination under anesthesia and endoscopic surgery (biopsy or transurethral resection) and imaging studies. The modifier "p" refers to pathologic staging based on cystectomy and lymph node dissection.
\(^d\)See Follow-Up After Cystectomy (BL-E).
\(^m\)See Principles of Chemotherapy Management (BL-G).
\(^n\)See Principles of Radiation Management of Invasive Disease (BL-H).
\(^*\)There are data to support equivalent survival rates, but not uniform consensus about the role of these approaches. Not all institutions have experience with these multidisciplinary treatment approaches which require a dedicated team.
FIGURE 3 Survival according to treatment group and whether patients had superficial muscle involvement (Stage T2 disease) or more advanced disease (Stage T3 or T4a)

From Jacobs, B. L. et al.
CA Cancer J Clin 2010;60:244-272.
BA06 trial

Randomly Allocated (N = 976)

Allocated to no CMV (n = 485)
- Lost to follow-up (n = 2)
- Still on therapy (n = 0)

Allocated to CMV (n = 491)
- Received allocated intervention of 3 cycles (n = 392)
- Did not receive allocated intervention (n = 99)
  - Received 2 cycles (n = 37)
  - Received 1 cycle (n = 33)
  - Received 4 cycles (n = 1)
  - Received 0 cycles (n = 28)
- Reasons
  - Renal toxicity effect/impaired function (n = 23)
  - Other toxicity effects of chemotherapy (n = 18)
  - Disease progression or early death (n = 14)
  - Refusal to continue treatment (n = 21)
  - Protocol errors/unspecified reason (n = 23)

Lost to follow-up (n = 4)
- Still on therapy (n = 0)

Analyzed (n = 485)

Analyzed (n = 491)

International Collaboration of Trialists on behalf of the Medical Research Council Advanced Bladder Cancer Working Party (now the National Cancer Research Institute Bladder Cancer Clinical Studies Group), the European Organisation for Research and Treatment of Cancer Genito-Urinary Tract Cancer Group, the Australian Bladder Cancer Study Group, the National Cancer Institute of Canada Clinical Trials Group, Finnbladder, Norwegian Bladder Cancer Study Group, and Club Urologico Espanol de Tratamiento Oncologico Group JCO 2011;29:2171-2177
RT +/- Chemotherapy in Muscle invasive Bladder Cancer

James ND, NEJM 2012

Figure 1. Enrollment and Outcomes.
Organ Preservation for Muscle-Invasive Bladder Cancer by Transurethral Resection

Dan Leibovici, et al
Fig 1. Arm 1 of RTOG 89-03 for the treatment of invasive bladder cancer with combined TURBT, chemotherapy, and radiation therapy for attempted bladder preservation.

Fig 2. Arm 2 of RTOG 89-03 for the treatment of invasive bladder cancer with combined TURBT and concurrent chemotherapy and radiotherapy for attempted bladder preservation.
<table>
<thead>
<tr>
<th>Study</th>
<th>Neoadjuvant Arm</th>
<th>Standard Arm</th>
<th>Patients (N)</th>
<th>Survival</th>
</tr>
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<tbody>
<tr>
<td></td>
<td>Cis/RT</td>
<td>RT</td>
<td>255</td>
<td>No difference</td>
</tr>
<tr>
<td></td>
<td>Cis/RT or preop RT+cystectomy</td>
<td>RT or preop RT+cystectomy</td>
<td>99</td>
<td>No difference</td>
</tr>
<tr>
<td></td>
<td>Cis/cystectomy</td>
<td>Cystectomy</td>
<td>121</td>
<td>No difference</td>
</tr>
<tr>
<td></td>
<td>CMV/RT or cystectomy</td>
<td>RT or cystectomy</td>
<td>976</td>
<td>5.5% difference in favor of CMV</td>
</tr>
<tr>
<td></td>
<td>M-VAC/cystectomy</td>
<td>Cystectomy</td>
<td>298</td>
<td>Benefit with M-VAC (P = 0.06)</td>
</tr>
<tr>
<td></td>
<td>M-VAC/cystectomy</td>
<td>Cystectomy</td>
<td>206</td>
<td>No difference</td>
</tr>
<tr>
<td></td>
<td>M-VEC/cystectomy</td>
<td>Cystectomy</td>
<td>171</td>
<td>No difference</td>
</tr>
<tr>
<td></td>
<td>Cis/5-FU/RT/cystectomy</td>
<td>Cystectomy</td>
<td>104</td>
<td>No difference</td>
</tr>
<tr>
<td></td>
<td>ADM/Cis/RT/cystectomy</td>
<td>RT/cystectomy</td>
<td>311</td>
<td>No difference, 15% benefit with ADM + Cis in T3–T4a</td>
</tr>
<tr>
<td></td>
<td>MTX/Cis/cystectomy</td>
<td>Cystectomy</td>
<td>317</td>
<td>No difference</td>
</tr>
<tr>
<td></td>
<td>CarboMV/cystectomy</td>
<td>Cystectomy</td>
<td>194</td>
<td>Benefit with CarboMV</td>
</tr>
</tbody>
</table>
Toxicity and mortality associated with neoadjuvant chemotherapy are acceptable. Available data suggest that for “average-risk” patients with cT2 cancer, the benefit of adding chemotherapy to local therapy is at best modest. Likewise, available studies suggest a much more substantial benefit for patients with high-risk disease, such as cT3b cancers. The quality of the surgery is a confounding factor in these studies. Meta-analysis of cisplatin-containing combination neoadjuvant chemotherapy trials revealed a 5% difference in favor of neoadjuvant chemotherapy. Unfortunately, in this case, in which small differences in survival can be seen, it is regrettable that the data on quality of life are inadequate.” Sternberg et al Eur Urol 2009.